CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074459

Trade Name : DICLOFENAC SODIUM DELAYED RELEASE TABLETS USP

Generic Name: Diclofenac Sodium Delayed Release Tablets USP, 25mg, 50mg and 75mg

Sponsor : Copley Pharmaceutical, Inc.

Approval Date: June 25, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074459

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074459

APPROVAL LETTER

ANDA 74-459

Copley Pharmaceutical, Inc.
Attention: W.E. Brochu, Ph.D.
Canton Commerce Center
25 John Road
Canton, MA 02021

Dear Sir:

This is in reference to your abbreviated new drug application dated January 19, 1994, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Diclofenac Sodium Delayed-release Tablets USP, 25, 50, and 75 mg.

Reference is also made to your amendments dated June 14, 1994; October 26, and November 17, 1995; October 3, October 11, November 19, and December 23, 1996; and January 2, March 14, and May 20, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Diclofenac Sodium Delayed-release Tablets 25 mg, 50 mg, and 75 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Voltaren® Delayed Release Tablets 25 mg, 50 mg, and 75 mg, respectively, of Geigy Pharmaceuticals. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

6/24/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

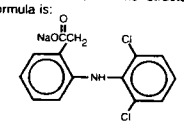
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074459

FINAL PRINTED LABELING

DESCRIPTION

Diclofenac sodium is a benzeneacetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt. The structural formula is:



M.W. 318.14 $C_{14}H_{10}Cl_2NNaO_2$

Diclofenac sodium, is a faintly yellowish white to light beige, virtually odorless, slightly hygroscopic crystalline powder. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in water and practically insoluble in chloroform and in dilute acid. The n-octanol/water partition coefficient is 13.4 at pH 7.4 and 1545 at pH 5.2. Diclofenac sodium has a dissociation constant (pKa) of 4.0 ± 0.2 at 25°C in water. Each enteric-coated tablet for oral administration contains 25, 50 and 75 mg of diclofenac sodium. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, red iron oxide, lactose monohydrate, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, povidone, sodium citrate, sodium hydroxide, sodium starch glycolate, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

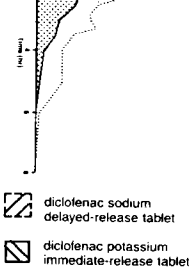
Pharmacodynamics

Diclofenac is a nonsteroidal anti-inflammatory drug [NSAID]. In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As, with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain related to inflammatory and primary dysmenorrhea. With regard to its analgesic effect, diclofenac is not a narcotic.

Pharmacokinetics

The therapeutic moiety, diclofenac, is available as diclofenac sodium delayed-release tablets and diclofenac potassium immediate-release tablets. These drug products differ in the cationic portion of the salt as well as in their release characteristics. Diclofenac potassium immediate-release tablets are formulated to release diclofenac in the stomach. Conversely, diclofenac sodium delayed-release tablets are in a pharmaceutic formulation that resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH-environment in the duodenum. The primary pharmacokinetic difference between the two products is in the pattern of drug release and absorption, as illustrated below:

± 1 SD plasma diclofenac concentrations after a single dose of a 50 mg diclofenac potassium immediate-release tablet (N=48) and a 50 mg diclofenac sodium delayed-release tablet (N=38)



diclofenac sodium delayed-release tablet

diclofenac potassium immediate-release tablet

Absorption

When diclofenac sodium delayed-release tablets are administered orally after fasting, diclofenac is completely absorbed from the gastrointestinal tract. Of this, only 50% of the absorbed dose of diclofenac from diclofenac sodium is systemically available, due to first-pass metabolism. Peak plasma levels are achieved in 2 hours in fasting normal volunteers, with a range from 1 to 4 hours. The area-under-the-plasma [illegible] (AUC) is dose [illegible] within the range of 25 mg to 150 mg. Peak plasma levels are less than dose-proportional and are approximately 1.0, 1.5, and 2 µg/mL for 25 mg, 50 mg and 75 mg doses, respectively. It should be noted that the administration of several individual diclofenac sodium tablets may not yield equivalent results in peak concentration as the administration of one tablet of a higher strength. This is probably due to the staggered gastric emptying of tablets into the duodenum. After repeated oral administration of diclofenac sodium 50 mg b.i.d., diclofenac did not accumulate in plasma.

When diclofenac sodium is taken with food, there is usually a delay in the onset of absorption of 1 to 4.5 hours, with delays as long as 10 hours in some patients, and a reduction in peak plasma levels of approximately 40%. The extent of absorption of diclofenac, however, is not significantly affected by food intake.

Distribution

Plasma concentrations of diclofenac decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac is reversibly bound to human plasma albumin.

A 4-week study, comparing plasma level profiles of diclofenac (diclofenac sodium 50 mg b.i.d.) in younger (26 to 46 years) versus older (66 to 81 years) adults, did not show differences between age groups (10 patients per age group). As with other NSAIDs, diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism and Elimination

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile.

Conjugates of unchanged diclofenac account for 5 to 10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. Conjugates of the principal metabolite account for 20 to 30% of the dose excreted in the urine and for 10 to 20% of the dose excreted in the bile. Conjugates of three other metabolites together account for 10 to 20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

Patients with Renal and/or Hepatic Impairment

To date, no differences, in the pharmacokinetics of diclofenac have been detected in studies of patients with renal (50 mg intravenously) or hepatic impairment (100 mg oral solution). In patients with renal impairment (N=5, creatinine clearance 3 to 42 mL/min), AUC values and elimination rates were comparable to those in healthy subjects. In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, N=10), diclofenac concentrations and urinary elimination values were comparable to those in healthy subjects.

Clinical Studies

Osteoarthritis:

Diclofenac sodium was evaluated for the management of the signs and symptoms of osteoarthritis of the hip or knee in a total of 633 patients treated for up to 3 months in placebo and active-controlled clinical trials against aspirin (N=449), and naproxen (N=92). Diclofenac sodium was given both in variable (100 to 150 mg/day) and fixed (150 mg/day) dosing schedules on either b.i.d. or t.i.d. dosing regimens. In these trials, diclofenac sodium was found to be comparable to 2400 to 3600 mg/day of aspirin or 500 mg/day of naproxen. Diclofenac was effective when administered as either b.i.d. or t.i.d. dosing regimens.

Rheumatoid Arthritis:

Diclofenac sodium was evaluated for managing the signs and symptoms of rheumatoid arthritis in a total of 468 patients treated for up to 3 months in placebo- and active-controlled clinical trials against aspirin (N=290), and ibuprofen (N=74). Diclofenac sodium was given in a fixed (150 or 200 mg/day) dosing schedule as either b.i.d. or t.i.d. dosing regimens. Diclofenac sodium was found to be comparable to 3600 to 4800 mg/day of aspirin, and 2400 mg/day of ibuprofen. Diclofenac sodium was used b.i.d. or t.i.d., administering 150 mg/day in most trials, but 50 mg q.i.d. (200 mg/day) was also studied.

Ankylosing Spondylitis:

Diclofenac sodium was evaluated for the management of the signs and symptoms of ankylosing spondylitis in a total of 132 patients in one active controlled clinical trial against [illegible] indomethacin [N=130]. Both diclofenac sodium and indomethacin patients were started on 25 mg t.i.d. and were permitted to increase the dose by 25 mg per day each week to a maximum dose of 125 mg/day. Diclofenac sodium 75 to 125 mg/day was found to be comparable to indomethacin 75 to 125 mg/day.

G.I. Blood Loss/Endoscopy Data:

G.I. blood loss and endoscopy studies were performed with diclofenac sodium delayed-release [enteric-coated] tablets that, unlike immediate-release tablets, do not dissolve in the stomach where the endoscopic lesions are primarily seen. A repeat-dose endoscopy study, in patients with rheumatoid arthritis or osteoarthritis treated with diclofenac sodium delayed-release tablets 75 mg b.i.d. (N=101), or naproxen (immediate-release tablets) 500 mg b.i.d. (N=103) for three months, resulted in a significantly smaller number of patients with an increase in endoscopy score from baseline and a significantly lower mean endoscopy score after treatment in the diclofenac sodium treated patients. Two repeat-dose endoscopic studies, in normal volunteers, showed that daily doses of diclofenac sodium delayed-release tablets 75 or 100 mg (N=6 and 14, respectively) for 1 week caused fewer gastric lesions and those that did occur had lower scores than those observed following daily 500 mg doses of naproxen (immediate-release tablets). In healthy subjects, the daily administration of 150 mg of diclofenac sodium (N=8) for 3 weeks resulted in a mean fecal blood loss of less than that observed with 3 g of aspirin daily (N=8). In four repeat-dose studies, mean fecal blood loss with 150 mg of diclofenac was also less than that observed with 750 mg of naproxen (n=8 and 6) or 150 mg of indomethacin (N=8 and 6). *The clinical significance of these findings is unknown since there is no evidence available to indicate that diclofenac sodium is less likely than other drugs of its class to cause serious gastrointestinal lesions when used in chronic therapy.*

Individualization of Dosage

Diclofenac, like other NSAIDs, shows interindividual differences in both pharmacokinetics and clinical response (pharmacodynamics). Consequently, the recommended strategy for initiating therapy is to use a starting dose likely to be effective for the majority of patients and to adjust dosage thereafter based on observation of diclofenac's beneficial and adverse effects.

In patients weighing less than 60 kg (132 lbs), or where the severity of the disease, concomitant medication, or other diseases warrant, the maximum recommended total daily dose of diclofenac should be reduced. Experience with other NSAIDs has shown that starting therapy with maximal doses in patients at increased risk due to renal or hepatic disease, low body weight (<60 kg), advanced age, a known ulcer diathesis, or known sensitivity to NSAID effects, is likely to increase frequency of adverse reactions and is not recommended (see PRECAUTIONS).

Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis:

The usual starting dose of diclofenac sodium delayed-release tablets for patients with osteoarthritis, is 100 to 150 mg/day, using a b.i.d. or t.i.d. dosing regimen. In two variable-dose clinical trials in osteoarthritis, of 266 patients started on 100 mg/day, 176 chose to increase the dose to 150 mg/day. Dosages above 150 mg/day have not been studied in patients with osteoarthritis.

The usual starting dose of diclofenac sodium for most patients with rheumatoid arthritis is 150 mg/day, using a b.i.d. or t.i.d. dosing regimen. Patients requiring more relief of pain and inflammation may increase the dose to 200 mg/day. In clinical trials, patients receiving 200 mg/day were less likely to drop from the trial due to lack of efficacy than patients receiving 150 mg/day. Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis because of increased risk of adverse events.

The recommended dose of diclofenac sodium delayed-release tablets for patients with ankylosing spondylitis is 100 to 125 mg/day, using a b.i.d. dosing regimen (see DOSAGE AND ADMINISTRATION regarding the 125 mg/day dosage regimen). In a variable-dose clinical trial, of 132 patients started on 75 mg/day, 122 chose to increase the dose to 125 mg/day. Dosages above 125 mg/day have not been studied in patients with ankylosing spondylitis.

INDICATIONS AND USAGE

Diclofenac sodium delayed-release tablets are indicated for acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

CONTRAINDICATIONS

Diclofenac sodium delayed-release tablets are contraindicated in patients with hypersensitivity to the product. Diclofenac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac have been reported in such patients.

WARNINGS

Gastrointestinal Effects

Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving diclofenac. Physicians and patients should therefore remain alert for ulceration and bleeding in patients treated chronically with diclofenac, even in the absence of previous G.I. tract symptoms. It is recommended that patients be maintained on the lowest dose of diclofenac possible consistent with achieving a satisfactory therapeutic response.

Risk of G.I. Ulcerations, Bleeding and Perforation with NSAID Therapy: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous G.I. tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper G.I. ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients for 3 to 6 months, and in about 2 to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious G.I. toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious G.I. events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal G.I. events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of G.I. toxicity.

Hepatic Effects

As with other NSAIDs, elevations of one or more liver tests may occur during diclofenac therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations, (i.e., less than 3 times the ULN [=the Upper Limit of the Normal range]), or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the hepatic enzymes, ALT (SGPT) is the one recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during diclofenac sodium treatment. In a large, open, controlled trial meaningful elevations of ALT and/or AST occurred in about 4% of 3700 patients treated for 2 to 6 months, including marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3 to 8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteo-arthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

In addition to the enzyme elevations seen in clinical trials, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, have been reported.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label), that involved 3700 patients monitored first at 8 weeks and 1200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with diclofenac. Based on this experience, if diclofenac is used chronically, the first transaminase measurement should be made no later than 8 weeks after the start of diclofenac treatment. As with other NSAIDs, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), diclofenac should be discontinued.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

PRECAUTIONS

General

Diclofenac Delayed-release Tablets should not be used concomitantly with other diclofenac containing

Diclofenac Sodium Delayed-release Tablets

LEA505300

Revised: August1996

LEA505300

products since they also circulate in plasma as diclofenac anion.

Allergic Reactions: As with other NSAIDs, allergic reactions including anaphylaxis, have been reported with diclofenac. Specific allergic manifestations consisting of swelling of eyelids, lips, pharynx and larynx, urticaria, asthma, and bronchospasm, sometimes with a concomitant fall in blood pressure (severe at times) have been observed in clinical trials and/or the marketing experience with diclofenac. Anaphylaxis has rarely been reported from foreign sources; in U.S. clinical trials with diclofenac in over 6000 patients, 1 case of anaphylaxis was reported. In controlled clinical trials, allergic reactions have been observed at an incidence of 0.5%. These reactions can occur without prior exposure to the drug.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking diclofenac. Therefore, as with other NSAIDs, diclofenac should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Renal Effects: As a class, NSAIDs have been associated with renal papillary necrosis and other abnormal renal pathology in long-term administration to animals. In oral diclofenac studies in animals, some evidence of renal toxicity was noted. Isolated incidents of papillary necrosis were observed in a few animals at high doses (20 to 120 mg/kg) in several baboon subacute studies. In patients treated with diclofenac, rare cases of interstitial nephritis and papillary necrosis have been reported (see ADVERSE REACTIONS).

A second form of renal toxicity, generally associated with NSAIDs, is seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAIDs results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate overt renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Cases of significant renal failure in patients receiving diclofenac have been reported from marketing experience, but were not observed in over 4000 patients in clinical trials during which serum creatinine and BUN values were followed serially. There were only 11 patients (0.3%) whose serum creatinine and concurrent serum BUN values were greater than 2.0 mg/dL and 40 mg/dL, respectively, while on diclofenac (mean rise in the 11 patients: creatinine 2.3 mg/dL and BUN 28.4 mg/dL).

Since diclofenac metabolites are eliminated primarily by the kidneys, patients with significantly impaired renal function should be more closely monitored than subjects with normal renal function.

Porphyria: The use of diclofenac in patients with hepatic porphyria should be avoided. To date, one patient has been described in whom diclofenac probably triggered a clinical attack of porphyria. The postulated mechanism, demonstrated in rats, for causing such attacks by diclofenac, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

Information for Patients

Diclofenac, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding and, more rarely, liver toxicity (see WARNINGS, Hepatic Effects) which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis and have a major role in the management of pain but they also may be commonly employed for conditions that are less serious. Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Because serious G.I. tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS, *Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy*). If diclofenac is used chronically, patients should also be instructed to report any signs and symptoms that might be due to hepatotoxicity of diclofenac; these symptoms may become evident between visits when periodic liver laboratory tests are performed (see WARNINGS, Hepatic Effects).

Drug Interactions

Aspirin: Concomitant administration of diclofenac and aspirin is not recommended because diclofenac is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations, peak plasma levels, and AUC values.

Anticoagulants: While studies have not shown diclofenac to interact with anticoagulants of the warfarin type, caution should be exercised, nonetheless, since interactions have been seen with other NSAIDs. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function as well, concurrent therapy with all NSAIDs, including diclofenac, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of diclofenac may increase serum concentrations of digoxin and methotrexate and increase cyclosporine's nephrotoxicity. Patients who begin taking diclofenac or who increase their diclofenac dose or any other NSAID while taking digoxin, methotrexate, or cyclosporine may develop toxicity characteristics of these drugs. They should be observed closely, particularly if renal function is impaired. In the case of digoxin, serum levels should be monitored.

Lithium: Diclofenac decreases lithium renal clearance and increases lithium plasma levels. In patients taking diclofenac and lithium concomitantly, lithium toxicity may develop.

Oral Hypoglycemics: Diclofenac does not alter glucose metabolism in normal subjects nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experiences of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac that necessitated changes in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Diuretics: Diclofenac and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7 to 10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline or digitoxin did not significantly affect the peak levels and AUC values of diclofenac.

Protein Binding

In vitro, diclofenac interferes minimally or not at all with the protein binding of salicylic acid (20% decrease in binding), tolbutamide, prednisolone (10% decrease in binding), or warfarin. Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence *in vitro* on the protein binding of diclofenac in human serum.

Drug/Laboratory Test Interactions

Effect on Blood Coagulation: Diclofenac increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are unlikely to be clinically important. Diclofenac is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day (12 mg/m^2/day, approximately the human dose) have revealed no significant increases in tumor incidence. There was a slight increase in benign mammary fibroadenomas in mid-dose-treated (0.5 mg/kg/day or 3 mg/m^2/day) female rats (high-dose females had excessive mortality), but the increase was not significant for this common rat tumor. A two-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m^2/day) in males and 1 mg/kg/day (3 mg/m^2/day) in females did not reveal any oncogenic potential. Diclofenac sodium did not show mutagenic activity in *in vitro* point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems, and was nonmutagenic in several mammalian *in vitro* and *in vivo* tests, including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. Diclofenac sodium administered to male and female rats at 4 mg/kg/day (24 mg/m^2/day) did not affect fertility.

Teratogenic Effects

There are no adequate and well controlled studies in pregnant women. Diclofenac should be used during pregnancy only if the benefits to the mother justify the potential risk to the fetus.

Pregnancy Category B: Reproduction studies have been performed in mice given diclofenac sodium (up to 20 mg/kg/day, or 60 mg/m^2/day) and in rats and rabbits given diclofenac sodium (up to 10 mg/kg/day, or 60 mg/m^2/day for rats, and 80 mg/m^2/day for rabbits), and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity in rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice and rats.

Labor and Delivery

The effects of diclofenac on labor and delivery in pregnant women are unknown. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of diclofenac during late pregnancy should be avoided and, as with other nonsteroidal anti-inflammatory drugs, it is possible that diclofenac may inhibit uterine contraction.

Nursing Mothers

Diclofenac has been found in the milk of nursing mothers. As with other drugs that are excreted in milk, diclofenac is not recommended for use in nursing women.

Pediatric Use

Safety and effectiveness of diclofenac in pediatric patients have not been established.

Geriatric Use

Of the more than 6000 patients treated with diclofenac in U.S. trials, 31% were older than 65 years of age. No overall difference was observed between efficacy, adverse event or pharmacokinetic profiles of older and younger patients. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS

Adverse reaction information is derived from blinded, controlled and open-label clinical trials, as well as worldwide marketing experience. In the description below, rates of more common events represent clinical study results; rarer events are derived principally from marketing experience and publications and accurate rate estimates are generally not possible.

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks with diclofenac sodium delayed-release tablets. By far the most common adverse effects were gastrointestinal symptoms, most of them minor, occurring in about 20%, and leading to discontinuation in about 3% of patients. Peptic ulcer, G.I. bleeding occurred in clinical trials in 0.6% (95%-confidence interval: 0.2% to 1%) of approximately 1800 patients during their first 3 months of diclofenac treatment and 1.6% (95%-confidence interval: 0.8% to 2.4%) of approximately 800 patients followed for 1 year.

Gastrointestinal symptoms were followed in frequency by central nervous system side effects such as headache (7%) and dizziness (3%). Meaningful (exceeding 3 times the Upper Limit of Normal) elevations of ALT (SGPT) or AST (SGOT) occurred at an overall rate of approximately 2% during the first 2 months of diclofenac sodium treatment. Unlike aspirin-related elevations, which occur more frequently in patients with rheumatoid arthritis, these elevations were more frequently observed in patients with osteoarthritis (2.6%) than in patients with rheumatoid arthritis (0.7%). Marked elevations (exceeding 8 times the ULN) were seen in 1% of patients treated for 2 to 6 months (see WARNINGS, Hepatic Effects).

The following adverse reactions were reported in patients treated with diclofenac:

Incidence Greater Than 1% - Causal Relationship Probable: (All derived from clinical trials.)

Body as a Whole: Abdominal pain or cramps," headache," fluid retention, abdominal distention.

Digestive: Diarrhea," indigestion," nausea," constipation," flatulence, liver tests abnormalities," PUB, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer (see above and also WARNINGS).

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special Senses: Tinnitus.

"Incidence 3% to 9% (incidence of unmarked reactions is 1 to 3%).

Incidence Less Than 1% - Causal Relationship Probable: The following reactions have been reported in patients taking diclofenac under circumstances that do not permit a clear attribution of the reaction to diclofenac. These reactions are being included as alerting information for physicians. Adverse reactions reported only in *worldwide marketing experience* or in the literature, not seen in clinical trials, are considered rare and are italicized.

Body as a Whole: Malaise, swelling of lips and tongue, photosensitivity, *anaphylaxis*, anaphylactoid reactions.

Cardiovascular: Hypertension, congestive heart failure.

Digestive: Vomiting, jaundice, melena, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, *hepatic necrosis*, appetite change, pancreatitis with or without concomitant hepatitis, *colitis*.

Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, *hemolytic anemia, aplastic anemia, agranulocytosis*, purpura, *allergic purpura*.

Metabolic and Nutritional Disorders: Azotemia.

Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability, *aseptic meningitis*.

Respiratory: Epistaxis, asthma, laryngeal edema.

Skin and Appendages: Alopecia, urticaria, eczema, dermatitis, *bullous eruption, erythema multiforme major*, angioedema, *Stevens-Johnson syndrome*.

Special Senses: Blurred vision, taste disorder, reversible hearing loss, scotoma.

Urogenital: *Nephrotic syndrome*, proteinuria, *oliguria, interstitial nephritis, papillary necrosis, acute renal failure*.

Incidence Less Than 1% - Causal Relationship Unknown (Adverse reactions reported only in worldwide marketing experience or in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Chest pain.

Cardiovascular: Palpitations, *flushing*, tachycardia, premature ventricular contractions, myocardial infarction.

Digestive: Esophageal lesions.

Hemic and Lymphatic: *Bruising*.

Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss*.

Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination*, convulsions, *disorientation, psychotic reaction*.

Respiratory: Dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages: Excess perspiration, *exfoliative dermatitis*.

Special Senses: Vitreous floaters, night blindness, amblyopia.

Urogenital: Urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

OVERDOSAGE

Worldwide reports on overdosage with diclofenac cover 66 cases. In approximately one-half of these reports of overdosage, concomitant medications were also taken. The highest dose of diclofenac was 5 g in a 17-year-old male who suffered loss of consciousness, increased intracranial pressure, aspiration pneumonitis, and died 2 days after overdose. The next highest doses of diclofenac were 4 g and 3.75 g. The 24-year-old female who took 4 g and the 28- and 42-year-old females, each of whom took 3.75 g, did not develop any clinically significant signs or symptoms. However, there was a report of a 17-year-old female who experienced vomiting and drowsiness after an overdose of 2.37 g of diclofenac.

Animal LD_{50} values show a wide range of susceptibilities to acute overdosage, with primates being more resistant to acute toxicity than rodents (LD_{50} in mg/kg - rats, 55; dogs, 500; monkeys, 3200).

In case of acute overdosage it is recommended that the stomach be emptied by vomiting or lavage. Forced diuresis may theoretically be beneficial because the drug is excreted in the urine. The effect of dialysis or hemoperfusion in the elimination of diclofenac (99% protein-bound; see CLINICAL PHARMACOLOGY) remains unproven. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption of diclofenac.

DOSAGE AND ADMINISTRATION

Diclofenac sodium may be administered as 25 mg, 50 mg, or 75 mg delayed-release tablets. Regardless of the indication, the dosage of diclofenac should be individualized to the lowest effective dose to minimize adverse effects (see CLINICAL PHARMACOLGY, Individualization of Dosage).

Osteoarthritis: The recommended dosage is 100 to 150 mg/day in divided doses, 50 mg b.i.d. or t.i.d. or 75 mg b.i.d. Dosages above 150 mg/day have not been studied in patients with osteoarthritis.

Rheumatoid arthritis: The recommended dosage is 150 to 200 mg/day in divided doses, 50 mg t.i.d. or q.i.d. or 75 mg b.i.d. Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis.

Ankylosing spondylitis: The recommended dosage is 100 to 125 mg/day administered as 25 mg q.i.d. with an extra 25 mg dose at bedtime if necessary. Dosages above 125 mg/day have not been studied in patients with ankylosing spondylitis.

HOW SUPPLIED

Diclofenac Sodium Delayed-release Tablets
25 mg - pink, round, unscored biconvex with beveled edges (debossed "Copley 431" on one side).

Bottles of 60
NDC 38245-431-66

Bottles of 100
NDC 38245-431-10

Bottles of 1000
NDC 38245-431-20

Diclofenac Sodium Delayed-release Tablets
50 mg - pink, round, unscored biconvex with beveled edges (debossed "Copley 474" on one side).

Bottles of 60
NDC 38245-474-66

Bottles of 100
NDC 38245-474-10

Bottles of 1000
NDC 38245-474-20

Diclofenac Sodium Delayed-release Tablets
75 mg - pink, round, unscored biconvex with beveled edges (debossed "Copley 427" on one side).

Bottles of 60
NDC 38245-427-66

Bottles of 100
NDC 38245-427-10

Bottles of 1000
NDC 38245-427-20

Do not store above 30°C (86°F). Protect from moisture. *Dispense in a tight, light-resistant container (USP).*

Caution: Federal law prohibits dispensing without prescription.

Copley Pharmaceutical, Inc.
Canton, MA 02021

Revised: August 1996
LEA505300

NDC 38245-431-20

Diclofenac Sodium Delayed-release Tablets

25 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 enteric-coated tablets

Copley Pharmaceutical, Inc.
Canton, MA 02021

Dispense in a tight, light-resistant container (USP).
Do not store above 30°C (86°F).
Protect from moisture.
Usual Dosage: See package insert.

N 3 38245-431-20 5

LOT: JUN 25 1997 RM 5339

EXP:

NDC 38245-431-10

Diclofenac Sodium Delayed-release Tablets

25 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 enteric-coated tablets

Copley Pharmaceutical, Inc.
Canton, MA 02021

Dispense in a tight, light-resistant container (USP).
Do not store above 30°C (86°F).
Protect from moisture.
Usual Dosage: See package insert.

N 3 38245-431-10 6

LOT: JUN 25 1997 RM 5340

EXP:

NDC 38245-431-68

Diclofenac Sodium Delayed-release Tablets

25 mg

CAUTION: Federal law prohibits dispensing without prescription.

60 enteric-coated tablets

Copley Pharmaceutical, Inc.
Canton, MA 02021

Dispense in a tight, light-resistant container (USP).
Do not store above 30°C (86°F).
Protect from moisture.
Usual Dosage: See package insert.

N 3 38245-431-68 7

LOT: JUN 25 1997 RM 5341

EXP:

NDC 38245-427-20

Diclofenac Sodium Delayed-release Tablets

75 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 enteric-coated tablets

Copley Pharmaceutical, Inc.
Canton, MA 02021

Dispense in a tight, light-resistant container (USP).
Do not store above 30°C (86°F).
Protect from moisture.
Usual Dosage: See package insert.
Pharmacist: Container closure is not child-resistant.

N 3 38245-427-20 8

LOT:
EXP: JUN 25 1997

RM 5333

NDC 38245-427-10

Diclofenac Sodium Delayed-release Tablets

75 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 enteric-coated tablets

Copley Pharmaceutical, Inc.
Canton, MA 02021

Dispense in a tight, light-resistant container (USP).
Do not store above 30°C (86°F).
Protect from moisture.
Usual Dosage: See package insert.

N 3 38245-427-10 9

LOT:
EXP: JUN 25 1997

RM 5334

NDC 38245-427-68

Diclofenac Sodium Delayed-release Tablets

75 mg

CAUTION: Federal law prohibits dispensing without prescription.

60 enteric-coated tablets

Copley Pharmaceutical, Inc.
Canton, MA 02021

Dispense in a tight, light-resistant container (USP).
Do not store above 30°C (86°F).
Protect from moisture.
Usual Dosage: See package insert.

N 3 38245-427-68 0

LOT:
EXP: JUN 25 1997

RM 5335

NDC 38245-474-68

Diclofenac Sodium Delayed-release Tablets

50 mg

CAUTION: Federal law prohibits dispensing without prescription.

60 enteric-coated tablets

Copley Pharmaceutical, Inc.
Canton, MA 02021

Dispense in a tight, light-resistant container (USP).
Do not store above 30°C (86°F).
Protect from moisture.
Usual Dosage: See package insert.

N 3 38245-474-68 4

LOT: JUN 25 RM 5338

EXP:

NDC 38245-474-10

Diclofenac Sodium Delayed-release Tablets

50 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 enteric-coated tablets

Copley Pharmaceutical, Inc.
Canton, MA 02021

Dispense in a tight, light-resistant container (USP).
Do not store above 30°C (86°F).
Protect from moisture.
Usual Dosage: See package insert.

N 3 38245-474-10 3

LOT: JUN 25 RM 5337

EXP:

NDC 38245-474-20

Diclofenac Sodium Delayed-release Tablets

50 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 enteric-coated tablets

Copley Pharmaceutical, Inc.
Canton, MA 02021

Dispense in a tight, light-resistant container (USP).
Do not store above 30°C (86°F).
Protect from moisture.
Usual Dosage: See package insert.
Pharmacist: Container closure is not child-resistant.

N 3 38245-474-20 2

LOT: JUN 25 RM 5336

EXP:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074459

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-459

3. NAME AND ADDRESS OF APPLICANT
Copley Pharmaceutical, Inc.
Attention: Bernie Grubstein
Canton Commerce Center
25 John Road
Canton, MA 02021

4. LEGAL BASIS FOR ANDA SUBMISSION:
Patent Certification: No outstanding patent
Patent Exclusivity: Expired on July 28, 1993

5. SUPPLEMENT(S): N/A 6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Diclofenac Sodium

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

January 19, 1994: Submission of application
October 11, 1996: Amendment
November 19, 1996: Amendment (telephone)
The two amendments are the subject of this review.
May 20, 1997 Telephone Amendment

10. PHARMACOLOGICAL CATEGORY
NSAID

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Enteric-coated tablets

14. POTENCY
25, 50, 75 mg

16. RECORDS AND REPORTS: N/A

17. COMMENTS:
See addendum to the review for the review of telephone amendment dated November 19, 1996

18. CONCLUSIONS AND RECOMMENDATIONS: Approvable

19. REVIEWER:
Dave Gill

DATE COMPLETED:
November 6, 1996

cc: ANDA 74-459
Division File
DUP File
Field Copy

Endorsements:
HFD-623/D.Gill/5-15-97 5-22-97
HFD-623/V.Sayeed/ 5/22/97
X:\new\firmsam\Copley/ltrs&rev\74459ap.d
F/T by: bc/5-21-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074459

BIOEQUIVALENCE REVIEW(S)

DW

ANDA 74-459

MAY 9 1997

Copley Pharmaceutical Inc.
Attention: Robert Kelly
25 John Road
Canton MA 02021

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Diclofenac Enteric-Coated Tablets, 25 mg, 50 mg, and 75 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted using USP 23 apparatus II paddles at 50 rpm using the following conditions:

Medium:	0.1 N HCl (120')
	Sodium phosphate buffer pH 6.8 (60')
Volume:	900 mL (acidic stage)
	900 mL (buffer stage)
Sampling Times:	Acidic stage: 30, 60, 120 min
	Buffer stage: 5, 10, 20, 30, 45, and 60 min
Tolerance (Q)	NMT 120 min (acidic stage)
	NLT 45 min (buffer stage)

3. The dissolution data presented by Copley using the revised conditions according to the latest guidance for Diclofenac issued by the Division of Bioequivalence dated October 6, 1994 was done using expired lots for the 75 mg, 50 mg and 25 mg tablets. The Division of Bioequivalence was informed by Copley that they have no current lots of the product available and do not plan to manufacture more diclofenac sodium until the submission is approved. Therefore, the Division of Bioequivalence is requesting that the firm supply dissolution data from their initial marketed batches to support the data from the expired lots.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DJ

JAN 14 1997

Diclofenac Sodium
75 mg Enteric-Coated Tablet
50 mg Enteric-Coated Tablet
25 mg Enteric-Coated Tablet
ANDA #74-459
Reviewer: Andre J. Jackson
WP #74459SDW.194

Copley Pharmaceutical
Canton Mass.
Submission Dated:
January 19, 1994
May 12, 1994

ADDENDUM TO REVIEW OF FASTING 75 MG,50 MG,25 MG ENTERIC-COATED TABLETS BIOEQUIVALENCE STUDIES AND POST-PRANDIAL 75 MG STUDY DISSOLUTION DATA AND WAIVER REQUEST FOR POST-PRANDIAL 50 MG AND 25 MG ENTERIC-COATED TABLET STUDIES

This addendum to the review contains corrected values for the confidence intervals for the 50 mg and 25 mg tablets.

REVIEW OF 50 MG FASTING STUDY

Objective:

The aim of this study is to compare the oral absorption of diclofenac sodium tablets manufactured by Copley Pharmaceutical with a commercial lot of the reference product, Voltaren^{R} enteric-coated tablets manufactured by Geigy following a single dose of 50 mg.

Methods:

The study was conducted by under the direction of . Samples were analyzed by under the direction of

I. Characterization of Study Group:

A. The subject inclusion and exclusion criteria were the same as for the 75 mg study.

B. The subject exclusion criteria were the same as for the 75 mg study.

C. Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions.

An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was done in 35, healthy males.

A. Subjects fasted overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Copley Pharmaceutical 50 mg diclofenac enteric-coated tablet, Lot # 474Z02, potency 98.4%.
2. Reference product: Geigy 50 mg Voltaren^{R} enteric-coated tablet, Lot # JT6421, potency 98.2%, expiration date August, 1996.

Table 10. Mean pharmacokinetic parameters and % CV for subjects that received either the test or reference diclofenac formulations (50 mg) following an overnight fast.

	TREATMENT				
Variable	A=Test	B=Reference	Ratio %A/B	N	Conf. Interval
AUCL[2] (ng/mlxhr)	1200.0±23.2	1234.1±23.9	97.2	35	
LNAUCL[4]	7.07	7.09	97.5	35	93-101%
AUCI[3] (ng/mlxhr)	1200.2±21.7	1251.1±25.0	96.3	32	
LNAUCI[4]	7.07	7.10	96.6	32	92-101%
CPEAK (ng/ml)	1275.2±30.0	1455.9±40.2	87.4	35	
LNCPEAK[4]	7.10	7.19	90.9	35	80-102%
KEL-1 (hr)	0.462±24.3	0.469±27.5		35	
HALF (hr)	1.61	1.62		35	
TPEAK (hr)	1.54	1.85		36	---
T LAG (hr)	0.87 ± 88.0	1.22±67.9	.71	35	49.8 -93.2%

Observed Mean ± CV%

[2]AUCL = AUC (0 to last measurable concentration)

[3]AUCI = AUC (0 -infinity)
[4]Log Transformed(LNAUCL, Cmax)

Table 15. Mean pharmacokinetic parameters and % CV for subjects that received either the test or reference diclofenac formulations (25 mg) following an overnight fast.

TREATMENT					
Variable	A=Test	B=Reference	Ratio %A/B	N	Conf. Interval
AUCL[2] (ng/mlxhr)	540.9±24.3	544.8±20.9	99.3	34	
LNAUCL[4]	6.26	6.28	98.4	34	93-103%
AUCI[3] (ng/mlxhr)	554.9±23.8	561.4±20.2	98.5	34	
LNAUCI[4]	6.29	6.31	97.6	34	93-102%
CPEAK (ng/ml)	665.85±37.3	686.7±29.2	97.0	34	
LNCPEAK[4]	6.43	6.49	94.2	34	84-105%
KEL-1 (hr)	0.490±33.14	0.535±39.0		34	
HALF (hr)	1.56	1.46		34	
TPEAK (hr)	1.68	1.85		34	---
T LAG (hr)	1.24 ± 71	1.61 ± 57.7	77.0	34	55.3 -100.9%

Subject Drop outs

The study began with 36 volunteers and there were two subject dropouts.

Observed Mean ± CV%

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 -infinity)
[4]Log Transformed(LNAUCL, Cmax)

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

1/14/97

Concur: _____
Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence

Date: 1/14/97

DN

JAN - 7 1997

Diclofenac Sodium
75 mg Enteric-Coated Tablet
50 mg Enteric-Coated Tablet
25 mg Enteric-Coated Tablet
ANDA #74-459
Reviewer: Andre J. Jackson
WP #74459C.D96

Copley Pharmaceutical
Canton Mass.
Submission Dated:
October 3, 1996
December 23, 1996

REVIEW OF SMALL-SCALE (12 SUBJECT) FASTING 75 MG ENTERIC-COATED TABLET BIOEQUIVALENCE STUDY .

Background

A bioequivalence study was submitted by the sponsor on January 19, 1994 which contained single dose fasting studies for their 75 mg, 50 mg and 25 mg enteric-coated tablets. The study also contained a 75 mg post-prandial study and waiver requests for food studies at the 50 mg and 25 mg dose levels. Analysis of the data indicated a longer lag time for the reference product. The firm informed the agency that the lag time for their product was in fact similar to the triangular shaped reference tablets manufactured by Ciba. Based upon this information an agreement was reached that the firm would submit a new 75 mg study in 12 subjects for their product vs the triangular shaped reference product. The current submission is the data from the small scale study.

Objective:

The aim of this study is to compare the absorption lag times of diclofenac sodium tablets manufactured by Copley Pharmaceutical with a commercial lot of the reference product, Voltaren^{R} enteric-coated tablets manufactured by Geigy following a single dose of 75 mg.

Methods:

The study was conducted by under the direction of
Samples were analyzed by under the direction of
Subjects were dosed on April 23, 1996 and May 7, 1996.

I. Characterization of Study Group:

A. Inclusion criteria

1. All volunteers selected for this study were male volunteers

between the ages of 18 and 45 years. Weight range of the volunteers was within 10% of normal body weight relative to height and frame size.

2. Each volunteer was given a general physical examination within 30 days of initiation of the study. Each examination included blood pressure, general observations, history, complete hemogram (hemoglobin, hematocrit, WBC, differential), urinalysis (including microscopic), biochemistry (blood urea nitrogen, serum bilirubin [total]), HIV antibody screen. Volunteers selected for the study had no clinically significant abnormal findings.

3. Normal electrocardiogram

B. Exclusion Criteria:

1. Volunteers with a history of alcohol or drug addiction during the past two years, gastrointestinal, renal, hepatic or cardiovascular disease, tuberculosis, epilepsy, asthma.

2. Any noted EKG abnormality.

3. Hypersensitivity or idiosyncratic reaction to diclofenac, aspirin or other NSAID's.

4. Participation in a previous clinical trial or the donation of one pint or more of blood within the past 90 days.

5. Use of any OTC medication on a regular basis.

6. Positive screen for drugs of abuse.

7. Positive HBsAg or HIV screen.

8. Subjects that smoke.

The consumption of alcohol-or xanthine-containing beverages and foods was prohibited for 24 hours before dosing and throughout the period of sample collection.

C. Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was done in 12 healthy males.

A. Subjects fasted overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Copley Pharmaceutical 75 mg diclofenac sodium enteric-coated tablet, Lot # 427Z02, potency 98.5%.

2. Reference product: Geigy 75 mg Voltaren^{R} enteric-coated tablet, Lot # KT6691, expiration date Dec 1997.

There was a 14 day washout between doses.

C. A 75 mg dose (1 x 75 mg) of each product (test and reference) was administered at time zero with 240 ml of water. The randomization scheme is presented in table 1.

Table 1. Random Assignment of 12 subjects

Sequence	SUBJECT
A,B	1,2,6,8,10,11
B,A	3,4,5,7,9,12

Treatment A: Diclofenac Tablets, 75 mg (1 Tablet) Copley

Treatment B: Voltaren Tablet, 75 mg (1 Tablet) Geigy

D.Plasma was collected pre-dose and at the following times post-dose:0.25, 0.5, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 4.75, 5.00, 5.25, 5.50, 5.75, 6.00, 6.50, 7.00, 8.00, 9.00, 10.0 and 12 hrs.

E. During the study subjects were monitored for adverse reactions.

III. Analytical

Assay sensitivity:

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported and lag time (i.e., the time at which the first measurable plasma concentration is observed).

Results

Table 2. Diclofenac plasma levels ng/ml (±cv) for the subjects that received the test and reference formulations (75 mg) after an overnight fast.

TREATMENT A Copley			TREATMENT B Reference	
Time (hrs)	Mean	CV%	Mean	CV%
0	0.00	0.00	0.00	0.00
0.25	59.92	267.4	2.14	346.4
0.5	202.07	247.9	105.82	344.7
0.75	372.36	163.7	298.85	302.0
1.0	635.57	124.0	568.08	144.1
1.25	962.25	70.6	641.85	136.7
1.50	1186.84	67.7	577.06	105.0
1.75	1009.53	67.6	602.16	118.5
2.00	677.69	61.8	548.68	153.8
2.25	460.36	75.2	330.65	132.2
2.50	324.81	67.2	516.75	150.1
2.75	216.82	62.3	498.83	140.0
3.00	152.04	55.7	472.59	135.4
3.25	120.09	53.0	3357.07	136.6
3.50	88.84	45.5	259.41	131.6
3.75	70.28	42.8	211.21	102.2
4.00	59.75	43.7	196.58	109.4
4.25	47.43	39.0	260.63	139.4
4.50	40.97	39.7	296.92	169.8
4.75	35.21	37.6	199.34	184.5
5.0	29.31	37.6	131.90	142.7
5.25	25.21	40.4	78.83	109.6
5.50	24.10	42.5	61.40	89.1
5.75	20.10	48.0	46.78	78.4
6.00	18.92	42.7	35.21	67.5
6.50	13.03	43.8	26.09	52.6
7.00	10.51	51.5	18.11	47.0
8.00	71.33	311.8	11.53	44.8
9.00	41.09	311.6	7.57	78.4
10.0	10.09	261.7	5.34	84.1

12.0	2.00	276.2	2.31	149.2

Table 3. Mean pharmacokinetic parameters and % CV for subjects that received either the test or reference diclofenac formulations following an overnight fast.

TREATMENT		
Variable	A=Test	B=Reference
AUCL[2] (ng/mlxhr)	1852.01±16.3	1882.18±18.7
LNAUCL[4]	1828.66	1849.58
AUCI[3] (ng/mlxhr)	1911.03±14.6	1900.40±18.7
LNAUCI[4]	1892.06	1867.64
CPEAK (ng/ml)	1680.13±34.4	2036.54±32.8
LNCPEAK[4]	1581.45	1929.08
TPEAK (hr)	2.02	2.27
T lag (hr)	1.42 ± 148.7	1.77 ±69.0

Observed Mean ± CV%

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 -infinity)
[4]Log Transformed-antilog of the geometric mean

Adverse Effects

Adverse effects are summarized in table 4.

Subject Drop outs

The study began with 12 volunteers and there were no drop outs.

Sample reassays:

2 samples out of 744 or 0.3% were reassayed primarily due to poor chromatography.

Comments:

1. The dissolution data presented with the previous study was found to be acceptable however, the dissolution conditions have been revised according to the latest guidance for Diclofenac issued by the Division of Bioequivalence dated

October 6, 1994.

The new dissolution specifications are as follows:

Apparatus:	USP XXIII paddle
RPM:	50
Medium:	0.1 N HCL (120')
	Sodium phosphate buffer pH 6.8 (60')
Volume:	900 ml (acidic stage)
	900 ml (buffer stage)
Sampling Times:	acidic stage: 30, 60, 120 min
	Buffer stage: 5, 10, 20, 30, 45, and 60 min
Tolerance (Q)	NMT 120 min (acidic stage)
	NLT 45 min (buffer stage)
Analytical	As per USP XXIII, if available or other validated method

2. The 90% confidence intervals for the 75 mg, 50 mg and 25 mg studies were found to be acceptable in the initial bioequivalence study.

3. The mean lag times for the test and reference products are within 30 minutes of each other.

4. The dissolution data presented by the firm using the revised conditions according to the latest guidance for Diclofenac issued by the Division of Bioequivalence dated October 6, 1994 was done using expired lots for the 75 mg , 50 mg and 25 mg tablets. The Division of Bioequivalence was informed by the firm that they have no current lots of the product available and do not plan to manufacture more diclofenac sodium until the submission is approved. Therefore, the Division of Bioequivalence is requesting that the firm supply dissolution data from their initial marketed batches to support the data from the expired lots.

Recommendation:

1. The fasting bioequivalence studies conducted by Copley Pharmaceutical on its 75 mg diclofenac sodium enteric coated tablet, lot 427Z02,comparing it to Geigy's Voltaren^{R} 75 mg enteric-coated tablet, also the study of its 50 mg diclofenac sodium enteric-coated tablet, lot 474Z02, comparing it to Geigy's Voltaren^{R} 50 mg enteric-coated tablet and finally the bioequivalence study conducted by Copley Pharmaceutical on its 25 mg diclofenac sodium enteric coated tablet, lot 431Z02 comparing it to Geigy's Voltaren^{R} 25 mg enteric-coated tablet have all been found to be acceptable by the Division of Bioequivalence. The post-prandial study conducted by Copley Pharmaceutical on its 75 mg diclofenac sodium enteric coated tablet, lot 427Z02,comparing it

to Geigy's Voltaren[R] 75 mg enteric-coated tablet has been found to be acceptable by the Division of Bioequivalence.. Therefore, Copley's 75 mg diclofenac sodium enteric-coated tablet is deemed bioequivalent to Geigy's Voltaren[R] 75 mg enteric-coated tablet.

2. The in vitro dissolution testings conducted by Copley Pharnmaceutical on its diclofenac sodium 75 mg enteric coated tablet, lot # 427Z02, on its diclofenac sodium 50 mg enteric coated tablet lot # 474Z02, and on its diclofenac sodium 25 mg enteric coated tablet lot # 431Z02 are acceptable. The firm has conducted an acceptable in vivo food-effects bioequivalence study (submission dated January 19, 1994) comparing its 75 mg enteric coated tablet of the test product with the 75 mg enteric coated tablet of the reference product Voltaren manufactured by Geigy. The formulations for the 50 mg and 25 mg enteric-coated tablets strengths are proportionally similar to the 75 mg strength of the test product which underwent food-effects bioequivalency testing. The waiver of in vivo food-effects bioequivalence requirements for the 50 mg enteric coated tablet and 25 mg enteric coated tablets are granted. The 50 mg and 25 mg enteric coated tablets are therefore deemed bioequivalent to the 50 mg and 25 mg enteric coated tablets of Voltaren manufactured by Geigy.

3. The in-vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted using USP XXIII apparatus II paddles at 50 rpm using the following conditions:

Medium:	0.1 N HCL (120')
	Sodium phosphate buffer pH 6.8 (60')
Volume:	900 ml (acidic stage)
	900 ml (buffer stage)
Sampling Times:	Acidic stage: 30, 60, 120 min
	Buffer stage: 5, 10, 20, 30, 45, and 60 min
Tolerance (Q)	NMT 120 min (acidic stage)
	NLT 45 min (buffer stage)

— Comment #3 should be forwarded to the firm.
40 H 1/6/97

Andre J. Jackson
Division of Bioequivalence
Review Branch I

Table 4. In Vitro Dissolution Testing

Drug (Generic Name):Diclofenac
Dose Strength:75 mg
ANDA No.:74-459
Firm:Copley Pharmaceutical
Submission Date:December 23, 1996
File Name:74459CDW.D95

I. Conditions for Dissolution Testing:Not a USP method,based on 1994 guidance

USP XXII Basket: Paddle:x RPM: 50
No. Units Tested: 12
Medium: 0.1N HCL Volume: 900 ml
Phosphate buffer pH 6.8 Volume: 900 ml
Specifications: NMT in 2 hrs in acid
NLT in 45 minutes in base
Reference Drug: Voltaren
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot # 427Z02 Strength(mg) 75			Reference Lot # KT6691 Strength(mg) 75		
	Mean %	Range	RSD	Mean %	Range	RSD
2 hrs (acid)	0.2		100	0.2		150
10 min	9.3		39.8	17.2		93
20 min	57.1		22.9	80.4		7.7
30 min	88.3		14.8	90.0		3.4
45 min	96.7		6.3	93.5		3.2

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot # 474Z02 Strength(mg) 50			Reference Lot # JT6421 Strength(mg) 50		
	Mean %	Range	RSD	Mean %	Range	RSD
2 hrs (acid)	0.3		150	0.1		100
10 min	4.4		47.7	13.5		75
20 min	43.1		19.7	76.6		6.2
30 min	78.2		14.5	84.7		4.4
45 min	96.3		3.8	88.5		4.2

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot # 431Z02 Strength(mg) 25			Reference Lot # JT4901 Strength(mg) 25		
	Mean %	Range	RSD	Mean %	Range	RSD
2 hrs (acid)	0.2		100	0.2		100
10 min	18.7		35.8	26.8		54
20 min	70.8		20.1	69.8		6.6
30 min	97.7		5.7	78.5		6.5
45 min	100.6		3.9	84.4		6.8

MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom Time after dosing	Dur-ation	Serious-ness	Caus-ality	Proba-bility	Report Method	Intensity at Onset	Forms Used	Follow-Up Time after dosing	Evolu-tion	Inten-sity	Action/Comment
Product Code A														
2	1	08:32am 23/APR/96	**Nausea**											
			1.6h	2.7h	NS	D	PR	SP	MO	None	3.9h	D	M	None
											4.2h	R	N/A	None
2	1	08:32am 23/APR/96	**Feels weak**											
			3.5h	45.0m	NS	O Undetermined cause	PO	SP	M	None	3.8h	N/A	N/A	BP = 90/70, pulse = 60 (irregular)
											4.2h	R	N/A	None
2	1	08:32am 23/APR/96	**Feels faint**											
			3.8h	27.0m	NS	D	PO	O	MO	None	3.8h	N/A	N/A	Put on supine postion with a cold face cloth on forehead. BP = 90/70, pulse = 60 (irregular)
											4.0h	D	M	BP = 110/68, pulse = 64
											4.2h	R	N/A	None
2	1	08:32am 23/APR/96	**Dizziness**											
			3.9h	18.0m	NS	D	PO	SP	M	None	4.2h	R	N/A	None

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med.Prescrip.		O=Other-MD's Comment	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Copley 1 x 75 mg diclofenac sodium enteric-coated tab.
B = Ciba Geneva (Voltaren) 1 x 75 mg diclofenac sodium enteric-coated tab.

TABLE C3

MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Causality	Probability	Report Method	Intensity at Onset	Forms Used	Follow-Up: Time after dosing	Evolution	Intensity	Action/Comment
Product Code B															
8	2	08:44am 07/MAY/96	Feels he has to vomit	2.7h	3.8h	NS	D	PR	SP	M	None	5.8h 6.5h	D R	M N/A	None None

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days h=Hours m=Minutes	PO=Physician Obs AC=Addit. Comment MP=Med.Prescrip.	S=Serious NS=Non-Serious	D=Drug P=Procedure O=Other	D=Definite PR=Probable PO=Possible U=Unlikely	E=Elicited SP=Spontaneous O=Observed	M=Mild MO=Moderate S=Severe	I=Increased U=Unchanged D=Decreased R=Resolved	N/A = Not Applicable N/R = Not Recorded

A = Copley 1 x 75 mg diclofenac sodium enteric-coated tab.
B = Ciba Geneva (Voltaren) 1 x 75 mg diclofenac sodium enteric-coated tab.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-459 SPONSOR : Copley Pharmaceutical
DRUG & DOSAGE FORM : Diclofenac Sodium
STRENGTH (s) : 75 mg, 50 mg, 25 mg
TYPE OF STUDY: (SD) SDF MULT OTHER
STUDY SITE: CLINICAL : ANALYTICAL :

STUDY SUMMARY : 75 mg

Parameter	test	ref	ratio	90% CI (log).
L Cmax(ng/ml)	7.58	7.56	1.01	90-114
L AUC(0-T) ngxhr/ml	7.63	7.61	1.01	99-105
L AUC(0-Inf)ngxhr/ml	7.64	7.62	1.01	99-105
Tmax hr	1.53	2.83		
Half-life hr	2.48	2.36		

DISSOLUTION : Paddle 50RPM
Conditions 0.1 N HCL(900ml) ; Phosphate buffer pH 6.8(900ml)

Time(min)	Test Mean(range)	Ref. Mean(range)
~~15~~ 2hrs acid	.1-.6	.05-1
~~30~~ 10 min	3-14	26-57
~~45~~ 20 min	36-76	70.4-88
30 min	60-102	84-93
45 min	79-101	86-97

Q = M MT in 2hrs. in acid
N LT in 45 min in base

PRIMARY REVIEWER : BRANCH : I

INITIAL : _____ _____ DATE : 1/6/97

BRANCH CHIEF : BRANCH :

INITIAL : _____ DATE : _____

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : _____ DATE : _____

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-459 SPONSOR :
DRUG & DOSAGE FORM : Diclofenac Sodium
STRENGTH (s) : 75 mg, 50 mg, 25 mg
TYPE OF STUDY: (SD) (SDF) MULT OTHER
STUDY SITE: CLINICAL : ANALYTICAL :

STUDY SUMMARY : 50 mg

	Parameter	test	ref	ratio	90% CI (log).
Ln	Cmax(ng/ml)	7.10	7.19	1.01	90-114
Ln	AUC(0-T) ngxhr/ml	7.07	7.09	1.01	98-105
Ln	AUC(0-Inf) ngxhr/ml	7.07	7.10	1.01	98-104
	Tmax hr	1.54	1.85		
	Half-life hr	1.61	1.62		

DISSOLUTION :
Conditions

Time(min)	Test Mean(range)	Ref. Mean(range)
~~15~~ 2hr 5 acid		
~~30~~ 10 min		
~~45~~ 20 min		
30 min		
45 min		
Q = NMT	in 2hrs acid	
NLT	in 45 min base	

PRIMARY REVIEWER : BRANCH : I

INITIAL : TT DATE : 1/6/87

BRANCH CHIEF : BRANCH : "

INITIAL : _____ DATE : _____

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : _____ DATE : _____

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-459
DRUG & DOSAGE FORM : Diclofenac Sodium
STRENGTH (s) : 75mg, 50mg, 25mg
SPONSOR : Copley Pharmaceuti
TYPE OF STUDY: (SD) SDF MULT OTHER
STUDY SITE: CLINICAL : ANALYTICAL :

STUDY SUMMARY : 25 mg

	Parameter	test	ref	ratio	90% CI (log).
Ln	Cmax(ng/ml)	6.43	6.49	94.2	90-114
Ln	AUC(0-T) ngxhr/ml	6.26	6.28	98.4	98-105
Ln	AUC(0-Inf) ngxhr/ml	6.29	6.31	97.6	98-104
	Tmax hr	1.68	1.85		
	Half-life hr	1.56	1.46		

DISSOLUTION : Paddle 50RPM
Conditions 0.1N HCl (900ml); phosphate buffer pH 6.8(900ml)

Time(min)	Test Mean(range)	Ref. Mean(range)
15 2hrs acid	—	
30 10 min	—	
45 20 min	—	—
30 min	—	—
45 min	—	-
Q = NMT / NLT in 2hrs acid in 45 min in buf	—	—

PRIMARY REVIEWER : BRANCH : I

INITIAL : TT DATE : 1/6/87

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OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-459 SPONSOR : Copley
DRUG & DOSAGE FORM : Diclofenac Sodium
STRENGTH (s) : 75 mg, 50 mg, 25 mg
TYPE OF STUDY: SD (SDF) MULT OTHER
STUDY SITE: CLINICAL : ANALYTICAL :

STUDY SUMMARY : 75 mg - Fed

	Parameter	test	ref	ratio R/T	90% CI (log).
Ln	Cmax(ng/ml)	7.46	7.17	90.7	—
Ln	AUC(0-T) ngxhr/ml	7.27	7.50	89.9	—
Ln	AUC(0-Inf) ngxhr/ml	7.42	7.52	90.1	
	Tmax hr	1.82	1.86	—	
	Half-life hr	6.47	5.00	—	

DISSOLUTION : N/A
Conditions

Time(min)	Test Mean(range)	Ref. Mean(range)
15		
30		
45		

Q =

PRIMARY REVIEWER : BRANCH :

INITIAL : _____ DATE : _____

BRANCH CHIEF : BRANCH :

INITIAL : _____ DATE : _____

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DIVISION OF BIOEQUIVALENCE

INITIAL : _____ DATE : _____

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

MAY 8 1995

Diclofenac Sodium
75 mg Enteric-Coated Tablet
50 mg Enteric-Coated Tablet
25 mg Enteric-Coated Tablet
ANDA #74-459
Reviewer: Andre J. Jackson
WP #74459SDW.194

Copley Pharmaceutical
Canton Mass.
Submission Dated:
January 19, 1994
May 12, 1994

REVIEW OF FASTING 75 MG,50 MG,25 MG ENTERIC-COATED TABLETS BIOEQUIVALENCE STUDIES AND POST-PRANDIAL 75 MG STUDY DISSOLUTION DATA AND WAIVER REQUEST FOR POST-PRANDIAL 50 MG AND 25 MG ENTERIC-COATED TABLET STUDIES

Background

Diclofenac sodium is an orally administered nonsteroidal anti-inflammatory drug(NSAID), which also has analgesic and antipyretic properties. Currently approved indications for diclofenac sodium are for acute or chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Diclofenac sodium is rapidly absorbed following oral administration with reported Tmax values of 1-3 hrs under fasting conditions. The reported Cmax ranged between 0.5-2 ug/ml. Area under the curve has been reported to increase linearly over the dose range 25-150 mg. Diclofenac sodium undergoes first-pass metabolism with a systemic availability of 50-60%. Reported terminal half-lives range between 0.5-4.3 hrs.

Diclofenac sodium is currently marketed as Voltaren® (Geigy) as 25, 50 and 75 mg enteric-coated tablets.

Objective:

The aim of this study is to compare the oral absorption of diclofenac sodium tablets manufactured by Copley Pharmaceutical with a commercial lot of the reference product, Voltaren® enteric-coated tablets manufactured by Geigy following a single dose of 75 mg.

Methods:

The study was conducted by under the direction of Samples were analyzed by under the direction of

I. Characterization of Study Group:

A. Inclusion criteria

1. All volunteers selected for this study were male volunteers between the ages of 18 and 45 years. Weight range of the volunteers was within 10% of normal body weight relative to height and frame size.

2. Each volunteer was given a general physical examination within 30 days of initiation of the study. Each examination included blood pressure, general observations, history, complete hemogram (hemoglobin, hematocrit, WBC, differential), urinalysis (including microscopic), biochemistry (blood urea nitrogen, serum bilirubin [total]), HIV antibody screen. Volunteers selected for the study had no clinically significant abnormal findings.

3. Normal electrocardiogram

B. Exclusion Criteria:

1. Volunteers with a history of alcohol or drug addiction during the past two years, gastrointestinal, renal, hepatic or cardiovascular disease, tuberculosis, epilepsy, asthma.

2. Any noted EKG abnormality.

3. Hypersensitivity or idiosyncratic reaction to diclofenac, aspirin or other NSAID's.

4. Participation in a previous clinical trial or the donation of one pint or more of blood within the past 90 days.

5. Use of any OTC medication on a regular basis.

6. Positive screen for drugs of abuse.

7. Positive HBsAg or HIV screen.

8. Subjects that smoke.

The consumption of alcohol- or xanthine-containing beverages and foods was prohibited for 24 hours before dosing and throughout the period of sample collection.

C. Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the

drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was done in 36, healthy males.

A. Subjects fasted overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Copley Pharmaceutical 75 mg diclofenac enteric-coated tablet, Lot # 427Z02, potency 98.5%.

2. Reference product: Geigy 75 mg Voltaren^{R} enteric-coated tablet, Lot # 1B161317,potency 96.7%, expiration date Feb 95.

There was a 7 day washout between doses.

C. A 75 mg dose (1 x 75 mg) of each product (test and reference) was administered at time zero with 240 ml of water. The randomization scheme is presented in table 1.

Table 1. Random Assignment of 26 subjects

Sequence	SUBJECT
A,B	1,2,6,7,8,9,12,13,16,18,19,21,25,27,29,30,33,34
B,A	3,4,5,10,11,14,15,17,20,22,23,24,26,28,31,32

Treatment A: Diclofenac Tablets, 75 mg (1 Tablet) Copley

Treatment B: Voltaren Tablet, 75 mg (1 Tablet) Geigy

The formulation for the 75 mg tablet is given in table 2.

Table 2. COMPOSITION OF THE 75 MG Diclofenac TABLET-See Attached

D. Plasma was collected pre-dose and at the following times post-dose: 0.5,0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 9, 10 and 12 hrs.

E. During the study subjects were monitored for adverse reactions.

III. Analytical

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

VI. Additional pharmacokinetic analysis

Since the formulation was an enteric-coated preparation, the confidence intervals for the individual input rates was calculated as was the 90% CI for the lag time.

Results

Table 3. Diclofenac plasma levels (±cv) for the subjects that received the test and reference formulations (75 mg) after an overnight fast.

	TREATMENT A Copley		TREATMENT B Reference	
Time (hrs)	Mean	CV%	Mean	CV%
0	0.00	0.00	0.00	0.00
0.5	339.76	221.9	000.00	00.0
0.75	584.05	151.4	0.748	600.0
1.0	807.73	102.5	4.33	579.9
1.33	925.19	91.8	154.40	536.5
1.67	847.01	86.3	352.49	236.3
2.00	736.00	86.4	678.21	139.5
2.33	502.44	117.6	841.23	99.5
2.67	294.72	96.0	725.08	83.8
3.00	201.82	95.2	766.08	93.5
3.33	260.89	239.2	604.06	102.2
3.67	187.79	170.8	410.64	104.0
4.00	183.33	221.6	364.31	133.5
4.33	149.32	252.8	318.84	154.4
4.67	85.41	153.6	244.67	157.7
5.00	58.98	102.9	160.50	169.4
5.33	42.87	79.3	117.42	183.7
5.67	34.22	71.1	74.27	142.3
6.0	34.12	131.2	53.37	110.8
6.5	22.6	69.6	36.40	101.2
7.0	17.71	53.1	27.67	87.5
8.0	12.25	44.2	16.99	59.2
9.0	9.09	45.5	12.27	53.3
10.0	7.65	47.3	10.43	66.7
12.0	3.98	86.3	5.39	68.2

Table 4. Mean pharmacokinetic parameters and % CV for subjects that received either the test or reference diclofenac formulations following an overnight fast.

TREATMENT					
Variable	A=Test	B=Reference	Ratio %A/B	N	Conf. Interval
AUCL[2] (ng/mlxhr)	2085.8±18.0	2048.6±18.9	101.8	36	
LNAUCL[4]	7.63	7.61	101.9	36	98.9 to 105%
AUCI[3] (ng/mlxhr)	2109.1±17.9	2072.8±18.9	101.8	36	
LNAUCI[4]	7.64	7.62	101.8	36	98.8 to 104.9%
CPEAK (ng/ml)	2100.8±32.9	2075.0±40.4	101.2	36	
LNCPEAK[4]	7.58	7.56	101.8	36	90.7 to 114.3%
KEL-1 (hr)	0.296± 27.0	0.314±26.9		36	
HALF (hr)	2.48	2.36		36	
TPEAK (hr)	1.53	2.83		36	---
T lag (hr)	1.07 ± 69.1	2.15 ±38.5		36	37 to 62.7%

Observed Mean ± CV%

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)
[4]Log Transformed(LNAUCL, Cmax)

Adverse Effects

Adverse effects are summarized in table 5.

Subject Drop outs

The study began with 36 volunteers and there were no drop outs.

Sample reassays:

18 samples out of 1800 or 1.0% were reassayed primarily due to

Dissolution

The dissolution study for diclofenac was done as follows:

Apparatus:	Paddle, 50 RPM
Medium:	1000 ml 0.1N HCL-120'
	1000 ml 0.05M phosphate buffer pH 7.5-45'
No. of Units Analyzed:	12
Specifications:	NMT in 120 minutes-acidic stage
	NLT in 45 minutes-buffer stage
Assay:	

The results are presented in table 6.

Deficiencies:

6.

Comments:

1. The dissolution data is acceptable.

Recommendation:

1. The bioequivalence study conducted by Copley Pharmaceutical on its 75 mg diclofenac enteric-coated tablet, lot 427Z02, comparing it to Geigy's Voltaren® 75 mg enteric-coated tablet has been found to be unacceptable by the Division of Bioequivalence.

REVIEW OF 50 MG FASTING STUDY

Objective:

The aim of this study is to compare the oral absorption of diclofenac sodium tablets manufactured by Copley Pharmaceutical with a commercial lot of the reference product, Voltaren® enteric-coated tablets manufactured by Geigy following a single dose of 50 mg.

Methods:

The study was conducted by under the direction of Samples were analyzed by under the direction of

I. Characterization of Study Group:

A. The subject inclusion and exclusion criteria were the same as for the 75 mg study.

B. The subject exclusion criteria were the same as for the 75 mg study.

C. Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was done in 35, healthy males.

A. Subjects fasted overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Copley Pharmaceutical ~~75~~ 50 mg diclofenac enteric-coated tablet, Lot # 474Z02, potency 98.4%.

2. Reference product: Geigy ~~75~~ 50 mg Voltaren® enteric-coated tablet, Lot # JT6421, potency 98.2%, expiration date August, 1996.

There was a 14 day washout between doses.

C. A 50 mg dose (1 x 50 mg) of each product (test and reference) was administered at time zero with 240 ml of water. The randomization scheme is presented in table 7.

Table 7. Random Assignment of 35 subjects

Sequence	SUBJECT
A,B	1,4,6,9,10,11,14,15,16,19,21,23,25,26,27,31, 32,34
B,A	2,3,5,7,8,12,13,17,18,20,22,24,28,29,30,33,3 5,36

Treatment A: Diclofenac Tablets, 50 mg (1 Tablet) Copley

Treatment B: Voltaren Tablet, 50 mg (1 Tablet) Geigy

The formulation for the 50 mg tablet is given in table 8.

Table 8. COMPOSITION OF THE 50 MG Diclofenac TABLET (See attached)

D. Plasma was collected pre-dose and at the following times post-dose: 0.25, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.25, 2.50, 2.75, 3, 3.25, 3.50, 3.75, 4, 4.25, 4.50, 4.75, 5, 5.25, 5.50, 6, 6.5, 7, 8, 9, 10 and 12 hours.

E. During the study subjects were monitored for adverse reactions.

III. Analytical

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

VI. Additional pharmacokinetic analysis

Since the formulation was an enteric-coated preparation, the confidence intervals for the individual input rates and the 90% CI for the lag time were calculated.

Results

Table 9. Diclofenac plasma levels (±cv) for the subjects that received the test and reference formulations (50 mg) after an overnight fast.

Treatment A COPLEY			Treatment B Reference	
Time (hrs)	Mean	CV%	Mean	CV%
0	0.00	0.00	0.00	0.00
0.25	38.57	499.6	0.956	294.1
0.50	290.82	186.2	27.23	538.3
0.75	417.32	130.0	169.08	241.5
1.00	480.85	100.4	481.96	133.8
1.25	488.31	101.1	589.35	111.1
1.50	427.04	108.0	525.08	85.7
1.75	388.34	99.5	576.08	103.8
2.00	363.93	107.4	424.26	109.2
2.25	315.85	105.0	285.53	105.8
2.50	269.09	123.3	310.04	101.7
2.75	223.36	128.9	315.38	182.6
3.00	187.73	161.0	211.70	109.5
3.25	135.82	138.0	191.54	121.0
3.50	106.50	118.2	156.09	155.6
3.75	90.08	109.7	112.75	112.3
4.00	91.93	162.6	100.65	135.1
4.25	97.52	221.7	97.76	196.2
4.50	70.84	187.9	69.76	150.8
4.75	48.2	139.1	49.17	99.6
5.0	36.70	121.9	36.57	66.1
5.25	29.96	101.7	29.85	60.7
5.5	25.49	81.3	25.20	50.7
5.75	21.36	76.1	21.87	45.1
6.0	19.00	73.4	19.53	42.1
6.5	14.81	62.0	15.87	41.7
7.0	10.93	66.8	11.59	42.5
8.0	8.20	107.5	7.32	75.8
9.0	5.11	135.3	5.35	116.0
10.0	3.48	166.8	2.53	149.3
12.0	1.79	325.9	0.509	327.1

Table 10. Mean pharmacokinetic parameters and % CV for subjects that received either the test or reference diclofenac formulations (50 mg) following an overnight fast.

TREATMENT					
Variable	A=Test	B=Reference	Ratio %A/B	N	Conf. Interval
AUCL[2] (ng/mlxhr)	1200.0±23.2	1234.1±23.9	101.8	36	
LNAUCL[4]	7.07	7.09	101.9	36	98.9 to 105%
AUCI[3] (ng/mlxhr)	1200.2±21.7	1251.1±25.0	101.8	36	
LNAUCI[4]	7.07	7.10	101.8	36	98.8 to 104.9%
CPEAK (ng/ml)	1200.2±21.7	1455.9±40.2	101.2	36	
LNCPEAK[4]	7.10	7.19	101.8	36	90.7 to 114.3%
KEL-1 (hr)	0.462±24.3	0.469±27.5		36	
HALF (hr)	1.61	1.62		36	
TPEAK (hr)	1.54	1.85		36	---
T LAG (hr)	0.87 ± 88.0	1.22±67.9	.71	36	49.8 - 93.2%

Observed Mean ± CV%

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)
[4]Log Transformed(LNAUCL, Cmax)

Adverse Effects

Adverse effects are summarized in table 11.

Subject Drop outs

The study began with 36 volunteers and there was one subject dropout.

Sample reassays:

38 samples out of 2170 or 1.7% were reassayed primarily due to the sample being designated as a pharmacokinetic outlier.

Dissolution

The dissolution study for diclofenac was done as follows:

Apparatus:	Paddle, 50 RPM
Medium:	1000 ml 0.1N HCL-120'
	1000 ml 0.05M phosphate buffer
	pH 7.5-45'
No. of Units Analyzed:	12
Specifications:	NMT in 120 minutes-acidic stage
	NLT in 45 minutes-buffer stage
Assay:	

The results are presented in table 6.

Deficiencies:

These data indicate that the test product exhibits a much faster absorption at the early time points.

3.

4. A graphical representation of the lag times for the subjects receiving the 50 mg dose (figure 2)(see attached), clearly shows that the test product is being absorbed as early as 0.5 hr post dose whereas the reference does not show significant number of subjects absorbing drug until 0.75 hours post dose.

5. The firm reported AUC(0-T) values which were 98-99% of those at AUC(inf). This may be a reasonable estimation since the reported half-life of the drug in 1-2 hours. However, it was apparent that the firm was using 3-10 time points to define the terminal log-linear phase which allows for an overestimation of the Ke since distribution data is included in the estimate. The Division of Bioequivalence suggests that for all future submissions, especially for drugs with half-lives longer than 2 hours, the firm establish an objective criterion such as the Akaike information criterion or utilize curve stripping to determine the proper number of points to be used to define the terminal phase. If this is not done the AUC(0-inf) values may be underestimated.

6. The firm did not give the lot size for the test formulation.

Comments:

1. The dissolution data is acceptable.

Recommendation:

1. The bioequivalence study conducted by Copley Pharmaceutical on its 50 mg diclofenac enteric-coated tablet, lot 474Z02, comparing it to Geigy's Voltaren^{R} 50 mg enteric-coated tablet has been found to be unacceptable by the Division of Bioequivalence.

REVIEW OF 25 MG FASTING STUDY

Objective:

The aim of this study is to compare the oral absorption of diclofenac sodium tablets manufactured by Copley Pharmaceutical with a commercial lot of the reference product, Voltaren® enteric-coated tablets manufactured by Geigy following a single dose of 25 mg.

Methods:

The study was conducted by under the direction of Samples were analyzed by under the direction of

I. Characterization of Study Group:

A. The inclusion criteria were the same as for the 75 mg study.

B. The exclusion criteria were the same as for the 75 mg study.

C. Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct:

The study was done in 35, healthy males.

A. Subjects fasted overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Copley Pharmaceutical 25 mg diclofenac enteric-coated tablet, Lot # 431Z02, potency 97.1%.

2. Reference product: Geigy 25 mg Voltaren[R] enteric-coated tablet, Lot # 1T002828, potency 99.6%, expiration date March, 1994.

There was a 14 day washout between doses.

C. A 25 mg dose (1 x 25 mg) of each product (test and reference) was administered at time zero with 240 ml of water. The randomization scheme is presented in table 12.

Table 12. Random Assignment of 35 subjects

Sequence	SUBJECT
A,B	1,4,5,6,8,11,14,16,19,20,21,24,25,28,31,32, 33,35
B,A	2,3,7,9,12,13,15,,17,18,22,23,26,27,29,30, 34,36

Treatment A: Diclofenac Tablets, 25 mg (1 Tablet) Copley

Treatment B: Voltaren Tablet, 25 mg (1 Tablet) Geigy

The formulation for the 25 mg tablet is given in table 13.

Table 13. COMPOSITION OF THE 25 MG Diclofenac TABLET
(See attached)

D. Plasma was collected pre-dose and at the following times post-dose: 0.25, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.25, 2.50, 2.75, 3, 3.25, 3.50, 3.75, 4, 4.25, 4.50, 4.75, 5, 5.25, 5.50, 6, 6.5, 7, 8, 9, 10 and 12 hours.

E. During the study subjects were monitored for adverse reactions.

III. Analytical

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

VI. Additional pharmacokinetic analysis

Since the formulation was an enteric-coated preparation, the confidence intervals for the individual input rates and the 90% CI for the lag time were calculated.

RESULT

Table 14. Diclofenac plasma levels (±cv) for the subjects that received the test and reference formulations (25 mg) after an overnight fast.

TREATMENT A Copley			TREATMENT B Reference	
Time (hrs)	Mean	CV%	Mean	CV%
0	0.00	0.00	0.00	0.00
0.25	6.25	340.2	4.46	446.4
0.50	22.26	292.6	71.41	299.5
0.75	89.42	204.1	99.64	267.5
1.00	280.82	128.0	119.93	193.9
1.25	350.90	82.0	141.85	164.2
1.50	305.79	88.6	137.29	140.7
1.75	178.10	104.5	174.95	122.3
2.00	118.91	85.0	257.41	119.8
2.25	83.98	84.3	177.42	95.4
2.50	60.32	75.5	161.90	95.4
2.75	74.13	159.3	133.89	98.4
3.00	99.29	156.6	101.56	103.6
3.25	107.36	155.9	75.67	91.7
3.50	91.07	145.8	78.01	150.2
3.75	66.60	166.4	69.93	207.3
4.00	48.58	147.3	87.47	187.9
4.25	36.21	114.8	69.74	196.5
4.50	29.02	97.9	51.46	181.4
4.75	21.81	79.2	33.59	149.3
5.0	16.88	75.2	25.24	138.0
5.25	13.17	65.9	19.19	119.2
5.5	11.78	59.9	15.79	110.4
5.75	10.21	59.4	12.87	96.3
6.0	8.04	71.7	10.78	94.2
6.5	6.37	88.1	8.28	72.5
7.0	4.04	100.5	5.79	98.1
8.0	2.73	103.2	3.40	128.2
9.0	0.65	274.3	1.24	227.9
10.0	0.15	583.1	0.16	583.1
12.0	-	-	-	-

Table 15. Mean pharmacokinetic parameters and % CV for subjects that received either the test or reference diclofenac formulations (25 mg) following an overnight fast.

TREATMENT					
Variable	A=Test	B=Reference	Ratio %A/B	N	Conf. Interval
AUCL[2] (ng/mlxhr)	540.9±24.3	544.8±20.9	99.3	35	
LNAUCL[4]	6.26	6.28	98.4	35	98.9 to 105%
AUCI[3] (ng/mlxhr)	554.9±23.8	561.4±20.2	98.5	35	
LNAUCI[4]	6.29	6.31	97.6	35	98.8 to 104.9%
CPEAK (ng/ml)	665.85±37.3	686.7±29.2	97.0	35	
LNCPEAK[4]	6.43	6.49	94.2	35	90.7 to 114.3%
KEL-1 (hr)	0.490±33.14	0.535±39.0		35	
HALF (hr)	1.56	1.46		35	
TPEAK (hr)	1.68	1.85		35	---
T LAG (hr)	1.24 ± 71	1.61 ± 57.7	77.0	35	55.3 - 100.9%

Observed Mean ± CV%

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)
[4]Log Transformed(LNAUCL, Cmax)

Adverse Effects

Adverse effects are summarized in table 16.

Subject Drop outs

The study began with 36 volunteers and there was one subject dropout.

Sample reassays:

43 samples out of 2170 or 1.9% were reassayed primarily due to the sample being designated as a pharmacokinetic outlier.

Dissolution

The dissolution study for diclofenac was done as follows:

Apparatus:	Paddle, 50 RPM
Medium:	1000 ml 0.1N HCL-120'
	1000 ml 0.05M phosphate buffer pH 7.5-45'
No. of Units Analyzed:	12
Specifications:	NMT in 120 minutes-acidic stage
	NLT . in 45 minutes-buffer stage
Assay:	UV Spectroscopy

The results are presented in table 6.

Deficiencies:

1. The firm did not provide the lot size for their 25 mg enteric-coated diclofenac tablet.

Comments:

1.

2.

3.

4. The firm reported AUC(0-T) values which were 98-99% of those at AUC(inf). This may be a reasonable estimation since the reported half-life of the drug in 1-2 hours. However, it was apparent that the firm was using 3-10 time points to define the terminal log-linear phase which allows for an overestimation of the Ke since distribution data is included in the estimate. The Division of Bioequivalence suggests that for all future submissions, especially for drugs with half-lives longer than 2 hours, the firm establish an objective criterion such as the Akaike information criterion or utilize curve stripping to determine the proper number of points to be used to define the terminal phase. If this is not done the AUC(0-inf) values may be underestimated.

5. The 90% confidence intervals for AUC(0-inf) and Cmax On the log transformed scale were within the acceptable limits of 80-125% of the reference.

6. The dissolution data is acceptable.

Recommendation:

1. The bioequivalence study conducted by Copley Pharmaceutical on its 25 mg diclofenac enteric-coated tablet, lot 431Z02, comparing it to Geigy's Voltaren® 25 mg enteric-coated tablet has been found to be incomplete by the Division of Bioequivalence.

REVIEW OF 75 MG POST-PRANDIAL STUDY

Objective:

The aim of this study is to compare the oral absorption of the 75 mg diclofenac enteric-coated sodium tablets manufactured by Copley Pharmaceutical with a commercial lot of the reference product, Voltaren® enteric-coated tablets manufactured by Geigy following a high fat meal.

Methods:

The study was conducted by under the direction of Samples were analyzed by under the direction of

I. Characterization of Study Group:

A. The inclusion criteria were the same as for the 75 mg study.

B. The exclusion criteria were the same as for the 75 mg study.

C. Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was done in 16, healthy males.

A. Subjects fasted 10 hours overnight and 30 minutes prior to scheduled dosing, subjects received a standard breakfast consisting of:

1. one buttered English muffin
2. one fried egg
3. one slice of Canadian bacon
4. one slice of American cheese
5. one serving of hash brown potatoes
6. one 8 oz. glass of whole milk
7. one small glass, 6 oz, orange juice

B. The subjects received the folowing treatments:

1. Copley 75 mg diclofenac sodium, lot 427Z02, administered under fasting conditions.

2. Copley 75 mg diclofenac sodium, lot 427Z02, administerd under fed conditions.

3. Geigy (Voltaren^{R}), lot 1B161317 under fed conditions.

There was a 7 day washout between doses.

C. A 75 mg dose (1 x 75 mg) of each product (test and reference) was administered at time zero with 240 ml of water.

D. Plasma was collected pre-dose and at the following times post-dose: 1,1.50,2,2.5,3,3.50,4.50,5,5.50,6,6.5,7,8,8.5,9, 10,11,12,13,14,15 and 16 hours.

E. During the study subjects were monitored for adverse reactions.

III. Analytical

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group.

Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

Results

Table 17.Diclofenac plasma levels (±cv) for the subjects that received the test and reference formulations after a high fat meal.

Test-Fasting TREATMENT A			TEST-FOOD TREATMENT B		Reference-Food TREATMENT C	
Time	Mean	%CV	Mean	%CV	Mean	%CV
0	0.0		0.0		0.0	
1.0 hr	798.81	143.3	0.918	400.0	0	0
1.5 hr	737.58	81.6	24.52	400.0	0	0
2.0 hr	742.15	87.1	19.14	400.0	2.38	400.0
2.5 hr	437.76	100.7	14.10	387.3	409.4	273.6
3.0 hr	217.54	112.0	10.99	368.8	96.24	279.5
3.5 hr	109.75	59.5	52.00	340.0	110.88	267.9
4.0 hr	71.09	48.8	177.42	313.1	318.09	176.7
4.5 hr	51.66	46.5	450.86	168.2	561.54	148.3
5 hr	34.46	40.9	527.03	138.6	815.16	122.5
5.5 hr	25.03	35.2	536.82	174.0	414.19	108.1
6.0 hr	21.23	33.9	195.14	119.3	217.64	148.5
6.5 hr	16.21	34.5	77.08	112.0	101.28	107.7
7 hr	11.84	33.0	43.61	96.7	58.68	91.8
7.5 hr	10.18	40.7	27.78	87.5	36.83	74.4
8 hr	8.7	33.3	20.14	84.1	28.24	66.9
8.5 hr	6.9	44.8	46.67	255.4	21.05	65.3
9.0 hr	6.23	60.8	28.94	228.9	17.46	72.4
10 hr	2.90	121.6	220.71	376.7	10.95	66.7
11.0 hr	1.48	181.0	36.16	227.6	7.60	67.4
12 hr	0.63	273.3	59.22	233.1	80.52	371.6
13 hr	0	0	17.27	200.9	17.72	320.1
14 hr	0	0	12.96	170.9	5.56	269
15 hr	0	0	40.07	326.8	3.14	248
16 hr	0	0	11.19	249.3	0.34	400.0

Table 18. Mean pharmacokinetic parameters and ± SD for subjects that received either the test or reference diclofenac sodium formulations following a high fat meal or the reference under fasting conditions.

	TREATMENT			
Variable	Reference-Food	Test-Food	Test-Fasting	Ratio B/A
LAUCL[2] (ng/mlxhr)	7.50±0.22	7.27±0.50	7.46±0.39	89.9
LAUCI[3] (ng/mlxhr)	7.52±0.22	7.42±0.44	7.47±0.39	90.1
LCPEAK (ng/ml)	7.46±0.46	7.17±0.74	7.32±0.46	90.7
KEL-1 (hr)	0.38±0.05	0.40±.09	0.42±0.08	
HALF (hr)	1.86	1.82	1.68	
TPEAK (hr)	5.00	6.47	1.60	

Observed Mean ± SD

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)

Subject Drop outs

The study began with 36 volunteers and there was one subject dropout.

Sample reassays:

43 samples out of 2170 or 1.9% were reassayed primarily due to the sample being designated as a pharmacokinetic outlier.

Dissolution

The dissolution study for diclofenac was done as follows:

Apparatus: Paddle, 50 RPM
Medium: 1000 ml 0.1N HCL-120'
1000 ml 0.05M phosphate buffer pH 7.5-45'
No. of Units Analyzed: 12
Specifications: NMT in 120 minutes-acidic stage
NLT in 45 minutes-buffer stage
Assay:

The results are presented in table 6.

Overall Recommendation:

1. The bioequivalence studies conducted by Copley Pharmaceutical on its 75 mg diclofenac sodium enteric coated tablet, lot 427Z02 and its 50 mg diclofenac sodium enteric-coated tablet, lot 474Z02, comparing it to Geigy's Voltaren® 50 mg enteric-coated tablet has been found to be unacceptable by the Division of Bioequivalence. The bioequivalence study conducted by Copley Pharmaceutical on its 25 mg diclofenac sodium enteric coated tablet, lot 431Z02 comparing it to Geighy's Voltaren® 25 mg enteric-coated tablet has been found to be incomplete by the Division of Bioequivalence. 75mg and

   The firm should receive deficiencies 1-7 for the 75 mg study, deficiencies 1-6 for the 50 mg study and deficiency 1 for the 25 mg study.

2. The <u>in vitro</u> dissolution testing conducted on the 75 mg strength (lot # 427Z02), the 50 mg strength(lot # 474Z02), and the the 25 mg tablet(lot # 431Z02) is acceptable. The formulations for the 50 mg and 25 mg enteric-coated tablets strengths are compositionally proportional to the 75 mg enteric-coated tablet hich underwent a bioequivalence study. However, the waiver for the food study requirement for the 25 mg tablet is denied since the 75 mg study was found to be unacceptable.

3. The <u>in-vitro</u> dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000ml 0.1N HCL at 37 C using USP apparatus II paddles at 50 rpm for 2 hours. The media is then changed to 1000 ml of phosphate buffer at pH 7.5 for 45 minutes. The test product should meet the following specifications:

   NMT in 2 hrs in 0.1N HCL
   NLT in 45 min in pH 7.5 phosphate buffer
   of the labelled amount of the drug in the dosage form is dissolved.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

10/11/94

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

5/8/95

Concur: _____ Date: 5/8/95
Rabindra N. Patnaik, Ph.D.
~~for Acting~~ Director,
Division of Bioequivalence

cc: ANDA 74-459 original, HFD-630, HFD-600 (OGD, Hare), HFC-130 (JAllen), HFD-652 (Jackson, Wu), Drug File.

AJJ/100794/ntp/WP #74459SDW.194

Table 6 . In Vitro Dissolution Testing

Drug (Generic Name):Diclofenac
Dose Strength:75 mg
ANDA No.:74-459
Firm:Copley Pharmaceutical
Submission Date:January 19, 1994
File Name:744859SDW.194

Conditions for Dissolution Testing:

USP XXII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.1 N HCL /0.05M phosphate buffer pH 7.5
Volume:1000 ml each medium
Specifications: NMT '120 min acidic
NLT '45 min buffer
Reference Drug: Voltaren
Assay Methodology

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 427Z02 Strength(mg) 75			Reference Product Lot # 1B161317 Strength(mg) 75		
	Mean %	Range	%CV	Mean %	Range	%CV
2 hrs	0.1		-	0.03		
10	13.4		31.3	7.2		80.6
20	59.9		18.0	71.8		14.5
30	88.0		11.6	93.3		4.7
45	96.5		3.86	99.0		1.7

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 293-068 Strength(mg) 50			Reference Product Lot # JT6421 Strength(mg) 50		
	Mean %	Range	%CV	Mean %	Range	%CV
2hrs	0.0		-	0.7		-
10	10.1		30.7	18.4		34.2
20	63.8		9.7	83.0		9.8
30	96.2		4.4	88.9		5.7
45	100.5		1.9	90.7		4.5

Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot # 431Z02 Strength(mg) 25			Reference Product Lot # 1T002828 Strength(mg) 25		
	Mean %	Range	%CV	Mean %	Range	%CV
2 hrs	0.2		-	0.0		-
10	24.3		31.7	28.7		59.9
20	85.4		12.6	94.5		7.65
30	100		1.3	98.2		4.0
45	100.5		1.5	100		3.0

Table 2

DICLOFENAC SODIUM ENTERIC-COAT TABLET, 75mg

ABLET- INGREDIENT LISTING	mg/tablet	
DICLOFENAC SODIUM	75.00 mg	75.00 Kg
MICROCRUSTALLINE CELLULOSE, NF		
LACTOSE, NF		
SODIUM STARCH GLYCOLATE, NF		
POVIDONE, USP		
ALCOHOL, SDA		
CROSCARMELLOSE SODIUM, NF		
TALC, NF		
MAGNESIUM STEARATE, NF		
total tablet wt =	300.0 mg	
total bulk =	rounded to nearest tenth	

COATING-		
METHACRYLIC COPOLUMER, NF		
CHROMATERIC pink colorant		
SODIUM HYDROXIDE, NF		
PURIFIED WATER, USP		
total tablet wt.=	324.0 mg	

Table 8

DICLOFENAC SODIUM ENTERIC-COAT TABLET, 50mg

TABLET- INGREDIENT LISTING

	mg/tablet	
DICLOFENAC SODIUM	50.00mg	50.00 Kg
MICROCRYSTALLINE CELLULOSE, NF		
LACTOSE, NF		
SODIUM STARCH GLYCOLATE, NF		
POVIDONE, USP		
ALCOHOL, SDA		
CROSCARMELLOSE SODIUM, NF		
TALC, NF		
MAGNESIUM STEARATE, NF		
total tablet wt =	200.0mg	

COATING

METHACRYLIC COPOLYMER, NF	
CHROMATERIC	
pink colorant	
SODIUM HYDROXIDE, NF	
PURIFIED WATER, USP	
total tablet wt.=	220.0 mg

TABLE 13

DICLOFENAC SODIUM ENTERIC-COAT TABLET 25mg

TABLET- INGREDIENT LISTING	mg/tablet
DICLOFENAC SODIUM	25.00 mg
MICROCRYSTALLINE CELLULOSE, NF	
LACTOSE, NF	
SODIUM STARCH GLYCOLATE, NF	
POVIDONE, USP	
ALCOHOL,	
CROSCARMELLOSE SODIUM, NF	
TALC, NF	
MAGNESIUM STEARATE, NF	
total tablet wt =	100.00 mg
total bulk =	

* evaporates during processing

COATING-

METHACRYLIC COPOLYMER, NF	
pink colorant	
SODIUM HYDROXIDE, NF	
PURIFIED WATER, USP	
total tablet wt.=	110.0 mg

FIGURE 1. TEST AND REFERENCE LAG TIME DISTRIBUTION

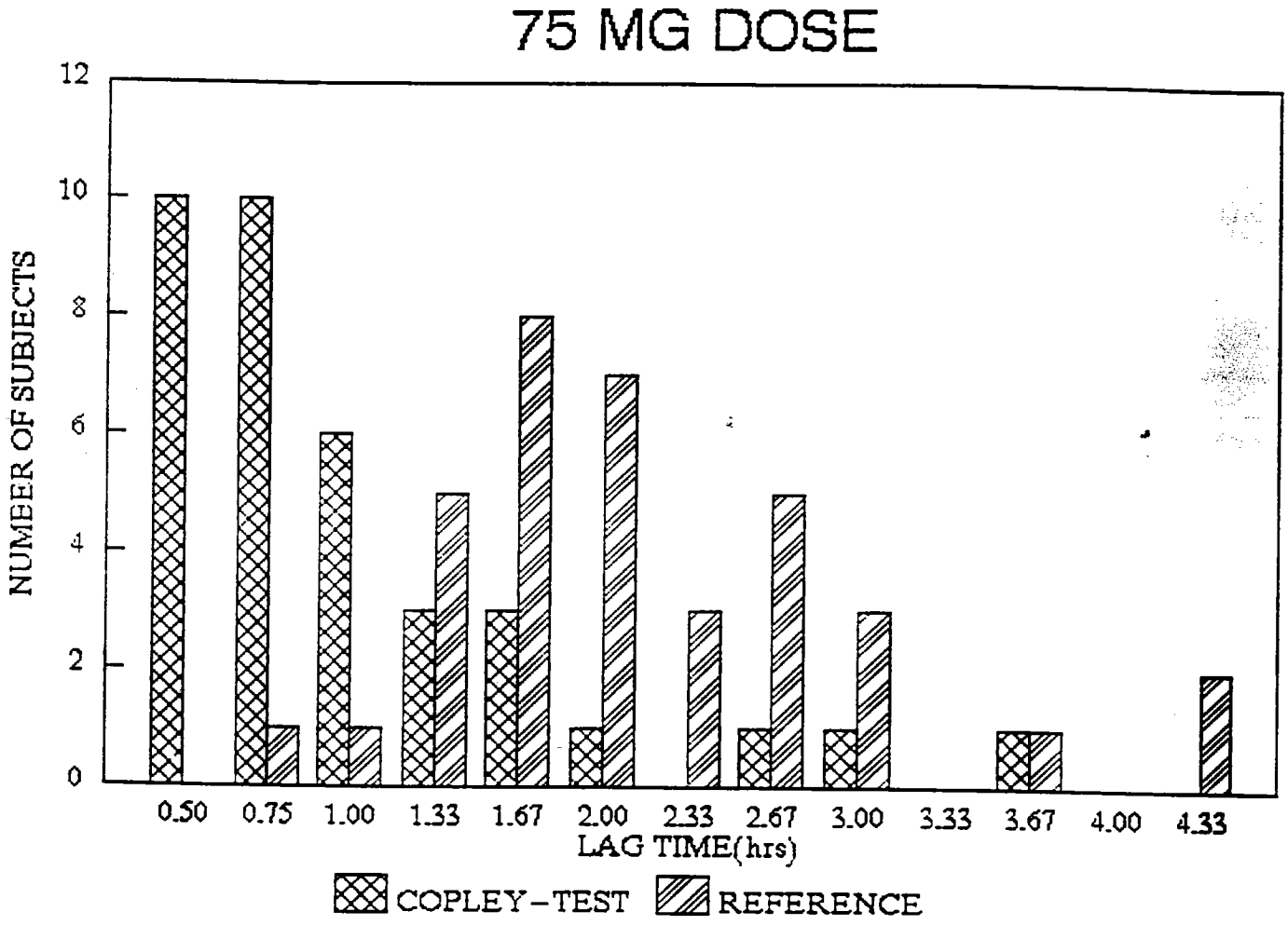

FIGURE 2. TEST AND REFERENCE LAG TIME DISTRIBUTION

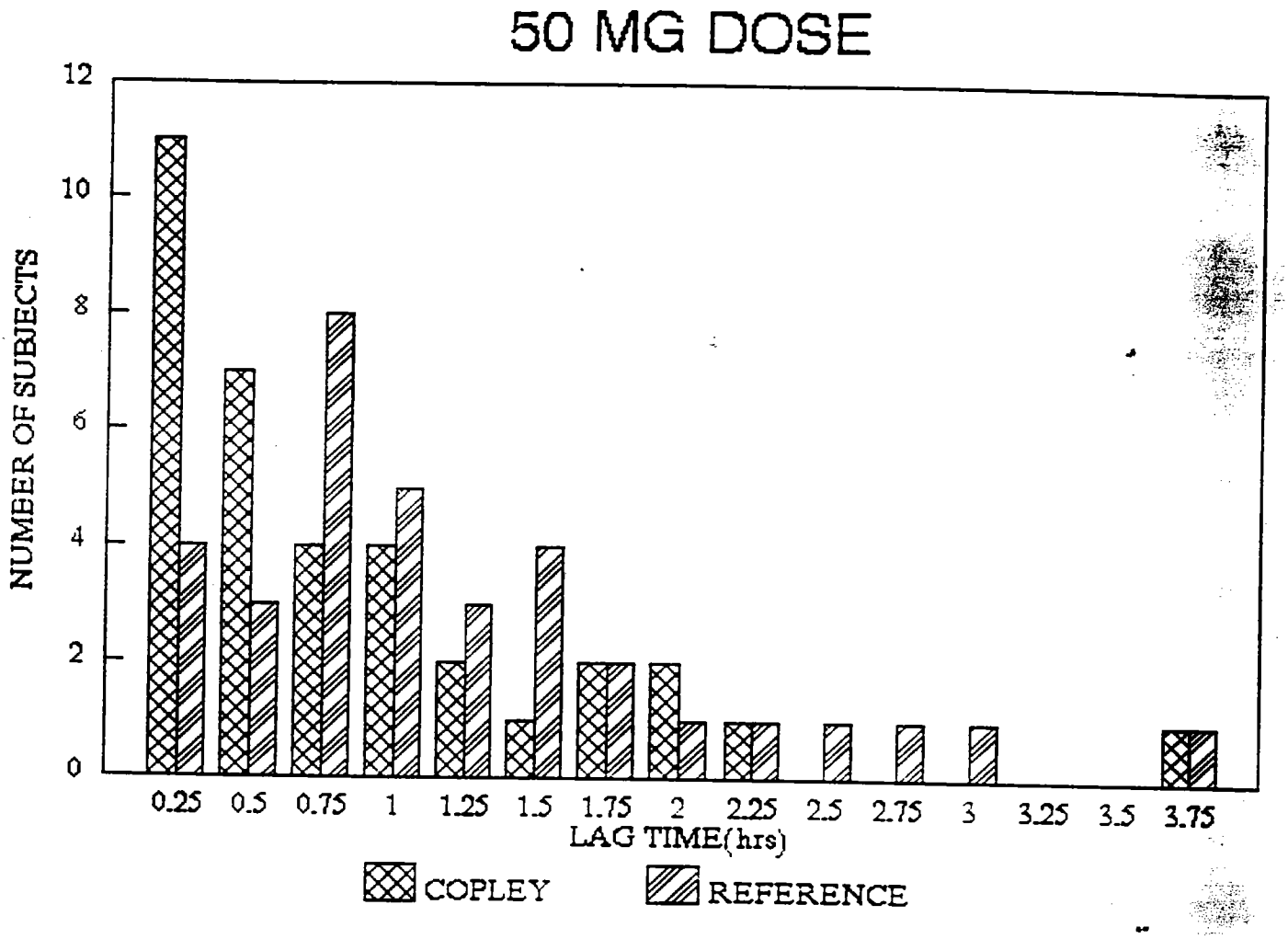

FIGURE3. TEST AND REFERENCE LAG TIME DISTRIBUTION

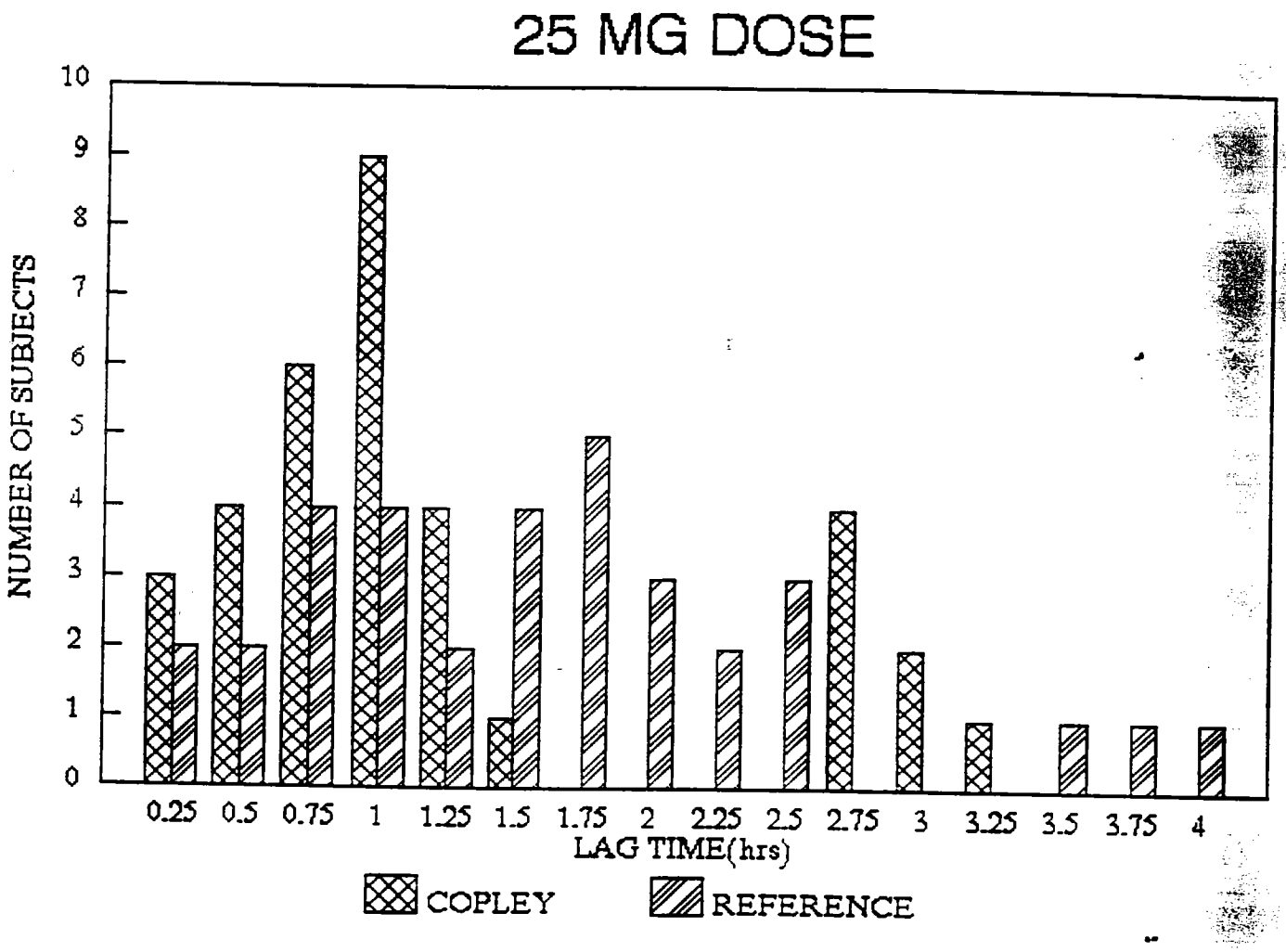

TABLE 5

CLINICAL REPORT NO. 920659

MEDICAL EVENTS - 75 mg Dose

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Follow-Up: Evolution	Follow-Up: Intensity	Follow-Up: Action / Comment
Product code A															
3	2	09:04: 19/09/93	**Headache**	4.2h	4.7h	NS	E	P	PR	SP	M	5.3h	U	M	None
												7.0h	U	M	None
												8.9h	R	N/A	
9	1	09:14: 12/09/93	**Runny nose**	2.5d	11.6d	NS	U	O	PR	E	M	6.4d	U	M	None
									Probable intercurrent infection						
												7.0d	U	M	None
												7.5d	D	M	None
												14.1d	R	N/A	
9	1	09:14: 12/09/93	**Sore throat**	2.5d	1.0d	NS	U	O	PR	E	M	3.5d	R	N/A	
									Probable intercurrent infection						

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Copley 1 x 75 mg diclofenac sodium enteric-coated tablet.
B = Geigy (Voltaren) 1 x 75 mg diclofenac sodium enteric-coated tablet.

000275

TABLE 5 CLINICAL REPORT NO. 920659

MEDICAL EVENTS

Subject	Period	Dosing	Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Follow-Up: Evolution	Follow-Up: Intensity	Follow-Up: Action / Comment
Product code B																
27	2	09:42:	19/09/93	**Swollen bruise on catheter site (left arm)**	1.4h	4.9d	NS	E	P	D	O	M	12.1h	D	M	None
													5.0d	R	N/A	
28	1	09:44:	12/09/93	**Bruised right eye**	4.7d	7.4d	NS	U	O	D	O	MO	7.0d	U	MO	None
									Post traumatic							
													7.5d	U	MO	None
													12.0d	R	N/A	
31	1	09:48:	12/09/93	**Feels hot (intermittent)**	1.0d	4.0d	NS	U	O	D	E	M	5.0d	R	N/A	
									Intercurrent infection							
31	1	09:48:	12/09/93	**Sore throat**	1.0d	6.4d	NS	U	O	D	E	M	6.9d	U	M	None
									Intercurrent infection							
													7.0d	U	M	None
													7.4d	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	1=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Copley 1 x 75 mg diclofenac sodium enteric-coated tablet.
B = Geigy (Voltaren) 1 x 75 mg diclofenac sodium enteric-coated tablet.

TABLE 5 CLINICAL REPORT NO. 920659

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Follow-Up: Evolution	Follow-Up: Intensity	Follow-Up: Action / Comment
Product code B															
31	1	09:48: 12/09/93	**Feels hot (intermittent)**	6.7d	8.8h	NS	U	O	D Intercurrent infection	E	M	6.9d	U	M	Temp.: 36.4°C, subject says woke up 4
												* 7.0d	R	N/A	times during night due to sweatiness
32	1	09:50: 12/09/93	**Stomach pain**	9.2h	1.0d	NS	E	D	PO	SP	M	12.3h 1.4d	D R	M N/A	None

TIME UNITS: d=Days, h=Hours, m=Minutes
SERIOUSNESS: S=Serious, NS=Non-Serious
LIKELIHOOD: E=Expected, U=Unexpected
CAUSALITY: D=Drug, P=Procedure, O=Other
PROBABILITY: D=Definite, PR=Probable, PO=Possible, U=Unlikely
REPORT METHOD: E=Elicited, SP=Spontaneous, O=Observed
INTENSITY: M=Mild, MO=Moderate, S=Severe
EVOLUTION: I=Increased, U=Unchanged, D=Decreased, R=Resolved
GENERAL: N/A = Not Applicable, N/R = Not Recorded

A = Copley 1 x 75 mg diclofenac sodium enteric-coated tablet.
B = Geigy (Voltaren) 1 x 75 mg diclofenac sodium enteric-coated tablet.

TABLE 11

MEDICAL EVENTS - 50 mg Study

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
4	1	08:03: 04/02/94	**Diarrhea (DIARRHEA/DIG)**	10.5d	1.5d	NS	U	O	PR	E	M	12.0d	R	N/A	
			Probable intercurrent infection												
4	1	08:03: 04/02/94	**Vomiting (VOMIT/DIG)**	10.5d	10.0m	NS	U	O	PR	E	M	10.5d	R	N/A	
			Probable intercurrent infection												
4	1	08:03: 04/02/94	**Vomiting (VOMIT/DIG)**	10.6d	10.0m	NS	U	O	PR	E	M	10.7d	R	N/A	
			Probable intercurrent infection												
13	2	08:12: 18/02/94	**Vomited (VOMIT/DIG)**	6.0m	1.0m	NS	U	O	PR	SP	MO	7.0m	R	N/A	Subject stated he did not see medication when vomiting
			Probable intercurrent GI infection												
21	1	08:20: 04/02/94	**Sore throat (PHARYNGITIS/RES)**	3.2d	22.0h	NS	U	O	PR	E	M	4.2d	R	N/A	
			Probable intercurrent infection												
21	1	08:20: 04/02/94	**Headache (HEADACHE/BODY)**	3.3d	5.0h	NS	U	O	PR	E	M	3.3d	N/R	N/R	Subject took 2 x 325 mg Tylenol tablets.
			Probable intercurrent infection									3.5d	R	N/A	
21	1	08:20: 04/02/94	**Liquid Stools (DIARRHEA/DIG)**	9.7d	4.6d	NS	U	O	PR	SP	M	14.0d	U	M	N/A
			Cause undetermined									14.3d	R	N/A	

TIME UNITS: d=Days, h=Hours, m=Minutes
SERIOUSNESS: S=Serious, NS=Non-Serious
LIKELIHOOD: E=Expected, U=Unexpected
CAUSALITY: D=Drug, P=Procedure, O=Other
PROBABILITY: D=Definite, PR=Probable, PO=Possible, U=Unlikely
REPORT METHOD: E=Elicited, SP=Spontaneous, O=Observed
INTENSITY: M=Mild, MO=Moderate, S=Severe
EVOLUTION: I=Increased, U=Unchanged, D=Decreased, R=Resolved
GENERAL: N/A = Not Applicable, N/R = Not Recorded

A 1 x Copley 50 mg diclofenac sodium enteric-coated tablet
B 1 x Geigy (Voltaren) 50 mg diclofenac sodium enteric-coated tablet

TABLE 11

MEDICAL EVENTS

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
21	1	08:20: 04/02/94	**Headache (HEADACHE/BODY)** (feels pain around left eye)	13.6d	11.0h	NS	U	O	PR	SP	M	14.0d	U	M	None
			Cause undetermined									14.1d	R	N/A	
24	2	08:23: 18/02/94	**Headache (HEADACHE/BODY)**	37.0m	9.0h	NS	U	O	PR	SP	M	4.3h	U	M	None
			Probable intercurrent infection									9.6h	R	N/A	
24	2	08:23: 18/02/94	**Dizziness (DIZZINESS/NER)**	2.2h	1.9h	NS	U	O	PR	SP	M	4.1h	R	N/A	
			Cause undetermined												
26	1	08:25: 04/02/94	**Body aches (PAIN/BODY)**	4.1d	2.3d	NS	U	O	PR	E	M	6.4d	R	N/A	
			Probable intercurrent infection												
26	1	08:25: 04/02/94	**Weakness (ASTHENIA/BODY)**	4.1d	2.3d	NS	U	O	PR	E	M	6.4d	R	N/A	
			Probable intercurrent infection												
32	1	08:31: 04/02/94	**Blocked nose (RHINITIS/RES)**	4.8d	2.3d	NS	U	O	PR	E	M	7.1d	R	N/A	
			Probable intercurrent infection												

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = 1 x Copley 50 mg diclofenac sodium enteric-coated tablet
B = 1 x Geigy (Voltaren) 50 mg diclofenac sodium enteric-coated tablet

TABLE 11

MEDICAL EVENTS

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Follow-Up: Evolution	Follow-Up: Intensity	Follow-Up: Action / Comment
Product code B															
1	1	08:02: 04/02/94	**Headache (HEADACHE/BODY)**	12.7d	2.0h	NS	U	O	D	E	M	12.7d	N/R	N/R	Subject took 2 x 325 mg Aspirin tablets.
			Cause undetermined									12.7d	R	N/A	
5	1	08:04: 04/02/94	**Feels faint (DIZZINESS/NER)**	3.4h	15.0m	NS	E	D	PO	O	M	3.6h	R	N/A	Cold compress on forehead
13	1	08:12: 04/02/94	**Nausea (NAUSEA/DIG)**	56.0m	16.0m	NS	U	O	PR	SP	M	1.1h	U	M	BP: 113/71 Pulse: 84
			Probable intercurrent GI infection									1.2h	R	N/A	
13	1	08:12: 01/02/94	**Vomited (VOMIT/DIG)**	57.0m	2.0m	NS	U	O	PR	SP	M	59.0m	R	N/A	
			Probable intercurrent GI infection												
14	1	08:12: 04/02/94	**Headache (HEADACHE/BODY)** (on top of head)	13.5d	19.0h	NS	U	O	PR	SP	M	14.0d	D	M	None
			Cause undetermined									14.0d	I	M	None
												14.2d	D	M	None
												14.2d	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = 1 x Copley 50 mg diclofenac sodium enteric-coated tablet
B = 1 x Geigy (Voltaren) 50 mg diclofenac sodium enteric-coated tablet

TABLE 11

MEDICAL EVENTS

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code B															
11	1	08:12: 04/02/94	**Vomited (VOMIT/DIG)**	14.0d	2.0m	NS	U	O	PR	SP	M	14.0d	R	N/A	
			Ok to dose. Probable intercurrent GI infection.												
24	1	08:23: 04/02/94	**Irritation of skin (RASH/SKIN)** on neck (right side)	9.6h	1.5h	NS	U	O	PR	SP	M	11.1h	R	N/A	
			Cause undetermined												
24	1	08:23: 04/02/94	**Headache (HEADACHE/BODY)** (front and left side)	15.9h	2.4d	NS	E	D	PO	E	M	3.0d	R	N/A	
24	1	08:23: 04/02/94	**Nasal congestion (RHINITIS/RES)**	3.2d	12.8d	NS	U	O	PR	E	M	14.0d	U	M	None
			Cause undetermined												
												14.0d	U	M	Temperature: 35.6°C
												14.0d	U	M	Temperature : 36.0°C
												14.2d	U	M	None
												14.5d	U	M	None
												16.0d	R	N/A	Subject took 2 tablespoons Triaminic DM after check out in period two.

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = 1 x Copley 50 mg diclofenac sodium enteric-coated tablet
B = 1 x Geigy (Voltaren) 50 mg diclofenac sodium enteric-coated tablet

TABLE 11

MEDICAL EVENTS

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code B															
24	1	08:23: 04/02/94	**Dry cough (COUGH DEC/RES)**	3.6d	12.4d	NS	U	O	PR	E	M	14.0d	U	M	None
			Cause undetermined									14.2d	U	M	None
												14.5d	U	M	None
												16.0d	R	N/A	Refer to ME, "Nasal congestion" resolution comment.
29	1	08:28: 04/02/94	**Runny nose (RHINITIS/RES)**	11.1d	8.8d	NS	U	O	PR	E	M	14.0d	U	M	Temperature : 36.4 °C
			Probable intercurrent infection									14.2d	D	M	None
												14.5d	U	M	None
												20.0d	R	N/A	
30	1	08:29: 04/02/94	**Fever (FEVER/BODY)**	8.1d	1.8d	NS	U	O	PR	E	M	9.9d	R	N/A	Subject states temperature: 101°F, 9 days post-dose
			Probable intercurrent infection												

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = 1 x Copley 50 mg diclofenac sodium enteric-coated tablet
B = 1 x Geigy (Voltaren) 50 mg diclofenac sodium enteric-coated tablet

TABLE 16

MEDICAL EVENTS

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Follow-Up: Evolution	Follow-Up: Intensity	Follow-Up: Action / Comment
Product code A															
14	1	08:13: 02/02/94	**Sweatiness (SWEAT/SKIN)**	3.3h	6.0m	NS	E	P	PR	SP	M	3.4h	U	M	Cold facecloth on forehead
			At time of bloodraw									3.4h	R	N/A	
11	1	08:30: 02/02/94	**Right hand feels cold (VASC DIS PERIPH/CV)**	3.5h	2.0h	NS	E	P	PR	SP	M	5.5h	R	N/A	
13	1	08:32: 02/02/94	**Headache (HEADACHE/BODY)**	4.1d	22.0h	NS	U	O	PR	E	M	5.1d	R	N/A	
			Cause undetermined. OK to dose.												

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d-Days	S-Serious	E-Expected	D-Drug	D-Definite	E-Elicited	M-Mild	I-Increased	N/A = Not Applicable
h-Hours	NS-Non-Serious	U-Unexpected	P-Procedure	PR-Probable	SP-Spontaneous	MO-Moderate	U-Unchanged	N/R = Not Recorded
m Minutes			O-Other	PO-Possible	O-Observed	S-Severe	D-Decreased	
				U-Unlikely			R-Resolved	

A = 1 x Copley 25 mg diclofenac sodium enteric-coated tablet
B = 1 x Geigy (Voltaren) 25 mg diclofenac sodium enteric-coated tablet

TABLE 16

MEDICAL EVENTS

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code B															
15	1	08:14: 02/02/94	**Redness around catheter site (right arm) (RASH/SKIN)**	2.5h	*	NS	E	P	PR	O	M	*	R	N/A	
			* Resolve time unknown. Resolved approx. 2 days post-dose.												
												9.1h	D	M	None
												12.1h	D	M	None
21	2	08:20: 19/02/94	**Headache (HEADACHE/BODY)**	10.0m	1.5h	NS	E	D	PR	SP	M	1.7h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = 1 x Copley 25 mg diclofenac sodium enteric-coated tablet
B = 1 x Geigy (Voltaren) 25 mg diclofenac sodium enteric-coated tablet

MEDICAL EVENTS – 25 mg Dose

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
14	1	08:13: 02/02/94	**Right hand cold (VASOSPASM/CV)**	32.0m	2.2h	NS	E	P	PR	O	M	2.7h	R	N/A	
14	1	08:13: 02/02/94	**Right hand red (RASH/SKIN)**	32.0m	9.3h	NS	E	P	PR	O	M	1.0h	U	M	None
												1.8h	D	M	Good radial and ulnar pulse felt
												2.0h	D	M	None
												2.8h	D	M	None
												9.0h	R	N/A	
14	1	08:13: 02/02/94	**Left hand cold (VASC DIS PERIPH/CV)**	45.0m	1.1h	NS	E	P	PR	O	M	1.8h	R	N/A	
14	1	08:13: 02/02/94	**Left hand red (RASH/SKIN)**	45.0m	4.5h	NS	E	P	PR	O	M	1.0h	U	M	None
												1.8h	D	M	Hand still red but warm to the touch. Has good radial and ulnar pulse.
												2.0h	D	M	None
												2.8h	D	M	None
												5.3h	R	N/A	

TIME UNITS: d=Days, h=Hours, m=Minutes
SERIOUSNESS: S=Serious, NS=Non-Serious
LIKELIHOOD: E=Expected, U=Unexpected
CAUSALITY: D=Drug, P=Procedure, O=Other
PROBABILITY: D=Definite, PR=Probable, PO=Possible, U=Unlikely
REPORT METHOD: E=Elicited, SP=Spontaneous, O=Observed
INTENSITY: M=Mild, MO=Moderate, S=Severe
EVOLUTION: I=Increased, U=Unchanged, D=Decreased, R=Resolved
GENERAL: N/A = Not Applicable, N/R = Not Recorded

A = 1 x Copley 25 mg diclofenac sodium enteric-coated tablet
B = 1 x Geigy (Voltaren) 25 mg diclofenac sodium enteric-coated tablet